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(54) Title: UREA DERIVATIVES AS INHIBITORS OF CCR-3 RECEPTOR

(57) Abstract: Urea and amide derivatives inhibit cell function of the chemokine receptor CCR-3. These compounds offer an ef-
fective means for treating a range of diseases thought to be mediated by the CCR-3 receptor. A variety of useful urea and amide
derivatives can be synthesized using liquid and solid-phase synthesis protocols.



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UREA DERIVATIVES AS INHIBITORS OF CCR-3 RECEPTOR

BACKGROUND OF THE INVENTION

The present invention relates to certain urea derivatives that are inhibitors of CCR-3 receptor activity, methods for preparing these compounds,
5 pharmaceutical compositions containing such compounds and methods for their use.

Chemokines are chemotactic cytokines that are produced by a variety of cells to attract leukocytes to sites of inflammation or lymphoid tissue. CCR-3 is a chemokine receptor that is expressed in a variety of cells, including, but not limited to, eosinophils, basophils, T cells and dendritic cells. See Ponath, P.D. *et al.*, *J. Exp. Med.* (1996) 183, 2437-2448; Yamada, H. *et al.*, *Biochem. Biophys. Res. Comm.* (1997) 231, 365-368; Sallusto, F. *et al.*, *Science* (1997) 277, 2005-2007; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. CCR-3 is also known as a co-receptor to HIV virus infection. See He, J. *et al.*, *Nature* (1997) 385, 645-649.

Several chemokines including eotaxin, eotaxin-2, RANTES, MCP-2, MCP-3, MCP-
15 4 bind to CCR-3 and activate cell functions such as intracellular Ca²⁺ mobilization, chemotactic response, superoxide anion generation and cell aggregation. See Forssmann, U. *et al.*, *J. Exp. Med.* (1997) 185, 2171-2176; Heath, H. *et al.*, *J. Clin. Invest.* (1997) 99, 178-184; Uguccioni, M. *et al.*, *J. Exp. Med.* (1996) 183, 2379-2384; Tenscher, K. *et al.*, *Blood* (1996) 88, 3195-3199; Sato, K. *et al.*, *Blood*
20 (1999) 93, 34-42. In particular, eotaxin exhibits a potent and specific chemotactic activity for eosinophils via binding to CCR-3, *in vitro* and *in vivo*. See Ponath, P. D. *et al.*, *J. Clin. Invest.* (1996) 97, 604-612.

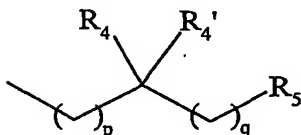
carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

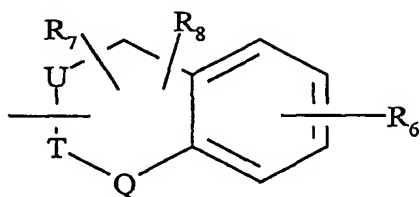
5 optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, 10 alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, 15 and heteroaryl

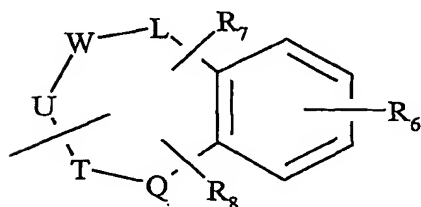
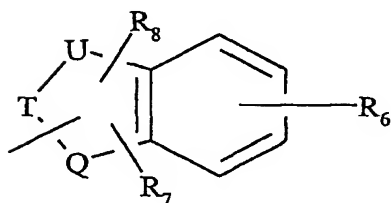
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino; 20

R₁ is:





or



or

p is 0, 1 or 2;

q is 0, 1 or 2;

5

R₄ and R₄' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy,

10 halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

15 and COR₉; wherein R₉ is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q , T , U , W and L are independently selected from the group of atoms consisting of C , N , O and S ; wherein adjacent atoms $U-T$, $T-Q$, $U-W$, $W-L$ may form one or more double bonds, and no pair of said adjacent atoms forms $O-O$ or $S-S$;

R_2 is selected from the group consisting of alkyl, alkenyl and alkynyl optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl,

5 arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

10 cycloalkyl

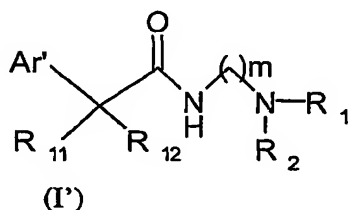
optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl,

15 arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

20 and heterocycle;

provided that no bond is formed between R₁ and R₂.

There is also provided, in accordance with a second aspect of the present invention, a compound having Formula (I'):



25 or a salt, hydrate, or stereoisomer thereof, wherein:

m is 2, 3, 4 or 5;

R₁₁ and R₁₂ are independently selected from the group consisting of hydrogen, halogen, C₁₋₅ alkyl, aryl and heteroaryl

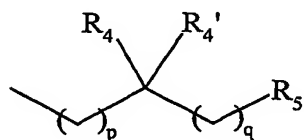
wherein the C₁₋₅ alkyl, aryl or heteroaryl is optionally substituted with one or
 5 more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₅alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino,
 10 hydroxyamino, amidino, guanidino, and cyanoguanidino;

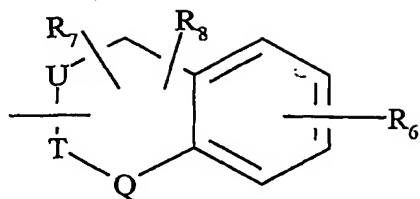
Ar' is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C₁₋₅alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl,
 15 arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, heteroaryl, benzyloxy, benzoyl and naphthoyl

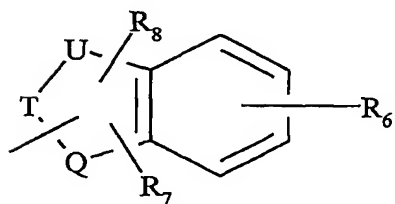
20 wherein the aryl, aryloxy, heteroaryl, benzyloxy, benzoyl or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
 25 alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₁ is:



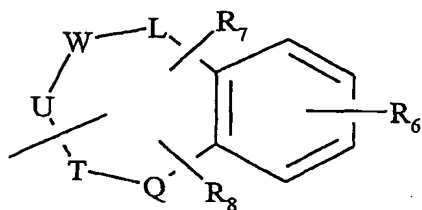


or



5

or



p is 0, 1 or 2;

q is 0, 1 or 2;

10 R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino

15

and COR₉, wherein R₉ is hydroxy, C₁₋₅alkyl, C₁₋₅alkoxy, amino, alkylamino or arylamino;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from
5 the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, and aryloxy
10 wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide,
15 arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl,
20 sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen,
25 trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and no pair of such adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ alkenyl and C₁₋₈ alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen, heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

10 C₁₋₅ alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

20 arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the suppression of eosinophil infiltration in bronchoalveolar lavage fluid (BALF) by Compound No. 12.

Figure 2 shows the suppression of eosinophil infiltration in bronchoalveolar lavage fluid (BALF) by Compound No. 87.

Scheme 1 is a representation of the synthesis of N-benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound No. 1).

Scheme 2 is a representation of the synthesis of 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound No. 13).

Scheme 3 is a representation of the synthesis of methyl 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate (Compound No. 27).

Scheme 4 presents the synthesis of 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoic acid (Compound No. 47).

Scheme 5 is a representation of the synthesis of [N-(3,4-dichlorophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane (Compound No. 53).

Scheme 6 presents the synthesis of 4-[[3-[(4-Chloroanilino)carbonylamino]propyl](6-methoxy-1-indanyl)amino]butanoic acid (Compound 63).

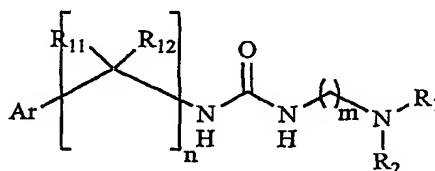
Scheme 7 presents the synthesis of 4-[[3-[2-[4-(Benzyloxy)-3-methoxyphenyl]acetylamino]propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 87).

Scheme 8 represents the formation of the acyl halide of (4-Benzyloxy-3-methoxyphenyl)acetic acid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

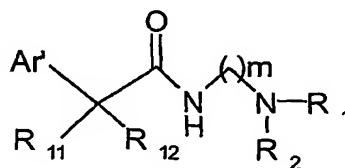
The present invention provides a new class of compounds which inhibit CCR-3 receptor activity. Because the CCR-3 receptor is understood to mediate a variety of diseases, the disclosed compounds, which are derived from urea, are useful for treating CCR-3-mediated diseases. Examples of such diseases include, without limitation, eosinophil-mediated diseases such as asthma, rhinitis, eczema, inflammatory bowel diseases, parasitic infections, and diseases that are mediated by T-cells, mast cells (Ochi H. et al., *J. Exp. Med.* (1999) 190:267-280, Romagnani P. et al., *Am. J. Pathol.* (1999) 155:1195-1204) and/or dendritic cells, such as autoimmune and inflammatory diseases and HIV infection.

In one embodiment of the present invention, there is provided a variety of compounds that inhibit cell function mediated by the chemokine receptor CCR-3. These compounds are urea derivatives with the formula depicted below as Formula I:



(I)

In another embodiment of the present invention, there is provided another variety of compounds that also inhibit cell function mediated by the chemokine receptor CCR-3. These compounds are amide derivatives of Formula (I') as depicted below:



(I')

The compounds of Formula (I) and (I'), as defined above, include variable groups such as an aryl group, a heteroaryl group and a heterocyclic group.

An aryl group is defined as a 6-15 membered aromatic carbocyclic moiety. This includes but is not limited to phenyl, naphthyl, anthryl, indenyl, phenanthrenyl and others.

A heteroaryl group is defined as a 5-15 membered aromatic ring system containing at least one hetero atom selected from the group consisting of N, O, and S. These include but are not limited to 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido- 2-, 3- or 4- pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido- 2-, 4- or 5-pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, triazinyl, oxotriazinyl, tetrazolo[1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indoliziny, quinoliziny, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

A heterocyclic group is defined as a 5-15 membered non-aromatic ring system containing at least one hetero atom selected from the group consisting of N, O, and S. These include but are not limited to hydrogenated derivatives of 2- or 3-thienyl, 2- or 3-furyl, 2- or 3- pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5- (1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5- (1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido- 2-, 3-

Ar is aryl or heteroaryl

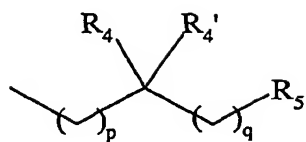
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkylloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

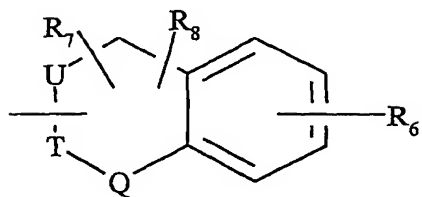
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₁ is:

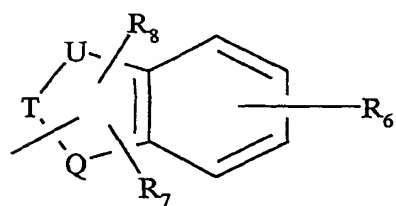


or

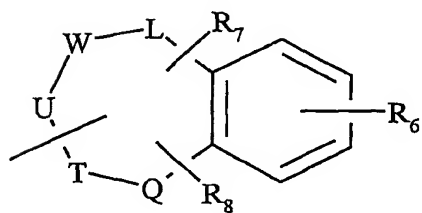


5

or



or



10

p is 0, 1 or 2;

q is 0, 1 or 2;

R₄ and R₄' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR₉; wherein R₉ is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino; R₈ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may

form one or more double bonds, and no pair of such adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from

5 the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, 10 alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from

the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, 15 alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen, 20 heteroaryl

optionally substituted with one or more groups independently selected from

the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, 25 arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen, arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen, cycloalkyl

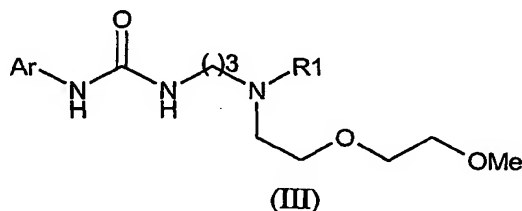
optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl,

acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen, and heterocycle;

provided that no bond is formed between R₁ and R₂.

- 5 In another example of the present invention, the family of compounds described above has cycloalkyloxy groups that are C₃₋₇ cycloalkyloxy groups, cycloalkyl groups that are C₃₋₇ cycloalkyl groups, alkoxy groups that are C₁₋₅ alkoxy groups, alkyl groups that are C₁₋₈ alkyl groups, alkenyl groups that are C₁₋₈ alkenyl groups and alkynyl groups that are
- 10 C₁₋₈ alkynyl groups.

In another embodiment of the present invention, there is provided another family of compounds which inhibit cell function mediated by the chemokine receptor CCR-3. In general these compounds have the Formula (III) depicted below.



- 15 or a salt, hydrate, stereoisomer, or complex thereof, wherein:

Ar is aryl or heteroaryl

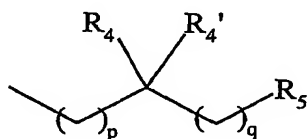
- optionally substituted with one or more groups independently selected from
- 20 the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₁ is:



p is 0, 1 or 2;

q is 0, 1 or 2;

R₄ and R₄' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino; and COR₆; wherein R₆ is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino; R₅ is aryl or heteroaryl

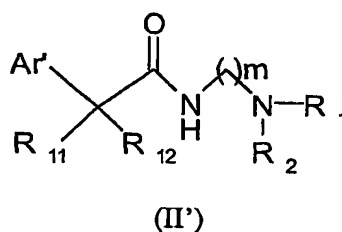
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino.

In another example of the present invention, the family of compounds described above has cycloalkyloxy groups that are C₃₋₇ cycloalkyloxy groups, cycloalkyl groups that are C₃₋₇ cycloalkyl groups, alkoxy groups that are C₁₋₅ alkoxy groups, alkyl groups that are C₁₋₈ alkyl groups, alkenyl groups that are C₁₋₈ alkenyl groups and alkynyl groups that are C₁₋₈ alkynyl groups.

In yet another embodiment of the present invention, there is provided a compound having Formula (II') as depicted below:



wherein:

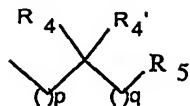
m is 3 or 4;

Ar' is aryl, optionally substituted with one or more groups independently selected from the group consisting of

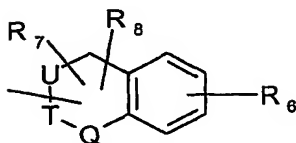
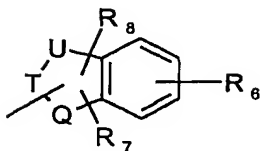
hydroxy, halogen, trihalomethyl, C₁₋₅alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, benzyloxy, benzoyl, and naphthoyl, wherein the aryl, aryloxy, benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C₁₋₅alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

R₁ is:



or



5

or

p is 0 or 1;

q is 0 or 1;

R₄ and R_{4'} is hydrogen, halogen, or C₁₋₃alkyl;

10 R₅ is aryl, optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, 15 alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino;

R₆ is hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl,

arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₇ and R₈ is independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

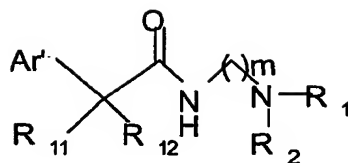
Q, T, U, W and L is independently selected from the group of atoms consisting of C, N, O and S. Two adjacent atoms of Q, T, U, W and L may make double bond(s), and no pair of such adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of C₁₋₃alkyl, C₁₋₃alkenyl and C₁₋₃alkynyl, wherein the C₁₋₃alkyl, C₁₋₃alkenyl or C₁₋₃alkynyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano;

provided that R₁ and R₂ do not form bond(s) with each other in Formula (II').

R₁₁ and R₁₂ are independently selected from the group consisting of hydrogen, halogen, and C₁₋₃alkyl.

In still another embodiment of the present invention, there is provided a compound having Formula (III') as depicted below:



(III')

wherein R₂ is selected from the group consisting of

- C₁-alkyl, C₁-alkenyl and C₁-alkynyl, optionally substituted with one or more
 5 groups independently selected from the group consisting of
 carboxy, carbamoyl, alkylcarbamoyl, alkylsulfonylcarbamoyl,
 alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido,
 arylsulfonamido, sulfonyl, alkylsulfonyl, sulfamoyl, alkylsulfamoyl,
 alkylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino,
 10 alkylamino, cyano,;

R₁ and R₂ do not form bond(s) with one another in Formula (III').

R₄, R₅, R₆, R₇, R₈, R₁₁, R₁₂, U, T, Q, p, and q have the same values as for Formula
 (II').

- In another embodiment of this invention, U, T and Q are carbon atoms; p
 15 and q are 0; R₁₁ and R₁₂ are hydrogen or C₁-alkyl.

Finally, an additional embodiment of the present invention provides for Ar'
 being aryl, optionally substituted with one or more groups independently selected
 from the group consisting of:

- hydroxy, halogen, trihalomethyl, C₁-alkyl, C₁-alkoxy, cyano, nitro, amino,
 20 carboxy, benzyloxy, benzoyl, naphthoyl, aryl, wherein benzyloxy, benzoyl, or
 naphthoyl is optionally substituted with one or more groups independently selected
 from the group consisting of:

hydroxy, halogen, trihalomethyl, C₁-alkyl, and C₁-alkoxy.

- The compounds of the present invention can be synthesized by various
 25 methods including, but not limited to, liquid phase or a solvent based synthesis and
 solid phase synthesis involving a polymeric resin.

The liquid phase synthesis generally involves addition of a substituted or unsubstituted alkyl amine containing compound to a protected amine containing starting material bearing a leaving group (e.g., Cl, Br, I, OTs, OMs, etc.). The resulting product bearing a protonated amine is reacted with an alkyl halide to yield
5 a substituted amine. Then, the protected amine moiety is deprotected by addition of base or, for example, hydrazine. The resultant free amine is reacted with a compound containing an isocyanate to yield the urea derivative.

A second synthesis involves the reaction of aromatic isocyanate with a haloalkylamine. The resultant product is then further reacted with an optionally
10 substituted amine containing compound, the amine of the optionally substituted amine containing compound is substituted by reaction with an alkyl halide to yield the aromatic urea derivative.

An additional method that can be used to prepare the present compounds involves reaction of a protected amine containing starting compound with an
15 alkylamine. The resultant diamine is reacted with an ester containing a leaving group, after deprotection, the aromatic urea derivative is formed by reaction with a compound containing an aromatic isocyanate.

The aromatic urea derivatives can be further derivatized by conventional organic synthesis techniques, for example, an ester can be converted to an acid by
20 addition of a metal hydroxide. Additionally, salts of the compounds can be formed by conventional synthetic techniques, such as addition to an amine moiety to form an ammonium salt.

Solid phase synthesis involves the use of polymeric resins. Reductive amination of the linker to the resin occurs by reacting a haloalkylamine with the
25 polymeric resin. The protonated amine is then protected by reaction with a substituted or unsubstituted acid chloride. The halogen of the original haloalkylamine is displaced by reaction with an alkyl amine compound and reductive amination follows by reaction with an aldehyde. The protected amine is deprotected by reaction with, for example, tin chloride, an acid or an amine. The deprotected

excipients include, but are not limited to, calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, vegetable oils and polyethylene glycol.

5 The form of the administered compound depends, in part, upon the use or the route of entry. Such forms should allow the agent to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological agents or compositions injected into the blood stream should be soluble in the concentrations used. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the compound or
10 composition from exerting its effect.

A compound of the present invention also can be formulated as a pharmaceutically acceptable salt, e.g., acid addition salt, and complexes thereof. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the agent without preventing its physiological effect.
15 Examples of useful alterations in physical properties include, but are not limited to, lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

A compound of the present invention can be administered to a mammal, including a human patient, using a variety of techniques. For example, for systemic
20 administration, oral administration or injection can be used. For oral administration, a compound of the present invention is formulated into conventional oral administration dosage forms such as capsules, tablets, and tonics. For injection, a compound is formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, a
25 compound can be formulated in a solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced. Examples of systemic administrations by injection include intramuscularly, intravenously, intraperitoneally and subcutaneously.

the patient. Examples of such instruments include, but are not limited to application devices, such as syringes or inhalers.

In yet another example, the claimed compounds are useful for treatment and/or prevention of rheumatoid arthritis. The treatment includes, but not limited to, administration of the claimed compounds through subcutaneous, intradermal, intramuscular, intraperitoneal, intravascular, and intracranial injections to human or other mammalian animal bodies.

EXAMPLES

10 SYNTHESIS OF ACTIVE COMPOUNDS

Example 1. Synthesis of N-Benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound 1)

The following synthesis is depicted in Scheme 1.

Step 1: To a mixture of 2-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in CH₃CN (50 ml) was added N-(3-bromopropyl)phthalimide (3.0 g, 11 mmol). The mixture was refluxed under stirring for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5 % methanol/chloroform) to afford N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 67%): MS(FD) m/e 343 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.74 (d, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.84 (m, 2H).

Step 2: To a mixture of N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 6.65 mmol) and potassium carbonate (1.8 g, 13 mmol) in CH₃CN (50 ml) was added ethyl iodide (1.6 ml, 20 mmol). The mixture was stirred at 70 °C for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2 % methanol/chloroform) to afford N-[3-[[2-(4-

chlorophenyl)ethyl](ethylamino)propyl]phthalimide (1.41 g, 57%): MS(ES⁺) m/e 371 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 3.71 (t, J = 7.3 Hz, 2H), 2.66 (m, 4H), 2.57 (m, 4H), 1.83 (m, 2H), 1.00 (t, J = 7.1 Hz, 3H).

5 Step 3: To a solution of N-[3-[[2-(4-chlorophenyl)ethyl](ethylamino)propyl]phthalimide (1.41 g, 3.8 mmol) in EtOH (20 ml) was added a solution of hydrazine monohydrate (1.5 g, 30 mmol) in EtOH (5 ml). The solution was stirred at RT for 4h, and then filtered. The filtrate was concentrated under vacuum to dryness. After adding water, the mixture was
10 extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave N-[2-(4-chlorophenyl)ethyl]-N-ethyl-1,3-diaminopropane (903 mg, 99%) which was used in the next step without further purification.

 Step 4: To a solution of N-[2-(4-chlorophenyl)ethyl]-N-ethyl-1,3-
15 diaminopropane (30 mg, 0.125 mmol) in CH₂Cl₂ (1 ml) was added benzyl isocyanate (20 mg, 0.15 mmol). After stirring at RT for 1h, the reaction mixture was adsorbed on a plate of silica gel and the plate was developed with 17% methanol/chloroform to afford N-benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (31.4 mg, 67%): MS(ES⁻) m/e 408 [M-H]⁻; ¹H NMR (400
20 MHz, CDCl₃) δ 7.27 (m, 4H), 7.23 (m, 3H), 7.08 (d, J = 8.5 Hz, 2H), 5.64 (br, 1H), 5.15 (br, 1H), 4.33 (d, J = 5.9 Hz, 2H), 3.24 (m, 2H), 2.72 (m, 4H), 2.62 (m, 4H), 1.68 (m, 2H), 1.04 (m, 3H).

 Compound 2, N-Benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,2-diaminoethane, can be obtained in an analogous manner to that described for
25 compound 1 and contains the following characteristics: MS(ES⁻) m/e 394 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (m, 4H), 7.22 (m, 3H), 7.06 (d, J = 8.5 Hz, 2H), 5.08 (br, 1H), 4.67 (br, 1H), 4.31 (d, J = 5.9 Hz, 2H), 3.18 (m, 2H), 2.63 (m, 4H), 2.55 (m, 4H), 0.97 (m, 3H).

Compound 44, Methyl 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoate, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES⁺) m/e 550 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.36 (m, 2H), 7.26 (bs, 4H), 7.20 (m, 1H), 5.03 (br, 1H), 4.40 (d, J = 6.1 Hz, 2H), 3.88 (m, 1H), 3.61 (s, 3H), 3.21 (m, 2H), 2.44 (m, 3H), 2.29 (m, 3H), 1.62 (m, 3H), 1.45 (m, 3H), 1.29 (d, J = 6.8 Hz, 3H).

Compound 45, Ethyl 6-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]hexanoate, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES⁺) m/e 578 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 2H), 7.26 (bs, 4H), 7.21 (dd, J = 8.3, 2.2 Hz, 1H), 4.72 (br, 1H), 4.38 (d, J = 6.1 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.85 (m, 1H), 3.15 (m, 2H), 2.43 (m, 4H), 2.27 (t, J = 7.3 Hz, 2H), 1.58 (m, 4H), 1.43 (m, 2H), 1.26 (m, 5H).

Compound 46, N-(2,4-Dichlorobenzylcarbonyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES⁺) m/e 442 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 2H), 7.29 (bs, 4H), 7.20 (m, 1H), 5.19 (m, 1H), 4.91 (br, 1H), 4.37 (d, J = 6.1 Hz, 2H), 3.89 (m, 1H), 3.15 (m, 2H), 2.63 (m, 1H), 2.51 (m, 3H), 1.62 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H), 1.05 (m, 3H).

Example 2. Synthesis of 4-[[3-(2-Methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 13)

The following synthesis is depicted in Scheme 2.

Step 1: N-(3-bromopropyl)phthalimide (3.5 g, 13 mmol) was added to a mixture of 1-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (1.8 g, 13 mmol) in CH₃CN (50 ml). The mixture was stirred at 70 °C for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 1.5 %

methanol/chloroform) to afford N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.1 g, 47%): MS(ES⁺) m/e 343 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (m, 2H), 7.72 (m, 2H), 7.23 (d, J = 1.5 Hz, 4H), 3.73 (m, 3H), 2.50 (m, 1H), 2.44 (m, 1H), 1.83 (m, 2H), 1.32 (d, J = 6.6 Hz, 3H).

Step 2: To a solution of N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (1.4 g, 4.1 mmol) in 20% EtOH/DMF (50 ml) were added succinic semialdehyde (15 wt. % solution in water, 5.0 ml, 8.2 mmol) and BAP (0.80 ml, 8.2 mmol), and the mixture was stirred at RT for 16 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[3-(phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.32 g, 75%): MS(ES⁺) m/e 429 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.75 (m, 2H), 7.26 (m, 4H), 4.05 (q, J = 6.8 Hz, 1H), 3.68 (m, 2H), 2.81 (m, 2H), 2.69 (m, 1H), 2.58 (m, 1H), 2.44 (t, J = 5.9 Hz, 2H), 2.01 (m, 2H), 1.82 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H).

Step 3: To a solution of 4-[[3-(phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (50 mg, 0.12 mmol) in EtOH (2 ml) was added hydrazine monohydrate (17 μl, 0.35 mmol), and the mixture was stirred at RT for 4 h. After adding chloroform (2 ml) and MeOH (1 ml), the reaction mixture was filtered, and the filtrate was concentrated under vacuum to dryness. After adding chloroform (1.5 ml) and DMF (0.7 ml) to the residue, 2-methylbenzyl isocyanate (28 μl, 0.20 mmol) was added, and the mixture was stirred at RT for 16 h. After adding water, the mixture was extracted with 10% methanol/chloroform, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 17% methanol/chloroform to afford 4-[[3-(2-methylbenzylureido)propyl][1-(4-

chlorophenyl)ethyl]amino]butanoic acid (24 mg, 45%): MS(ES⁺) m/e 468
[M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 2H), 7.28 (m, 2H), 7.09 (m, 4H), 6.30 (br, 1H), 4.33 (d, J = 3.4 Hz, 2H), 4.14 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.92 (m, 1H), 2.82-2.65 (m, 3H), 2.31 (s, 3H), 2.30 (m, 2H), 1.84-1.67 (m, 4H), 1.50 (d, J = 6.8 Hz, 3H).

Compound 4, 4-[[3-[1-(4-Bromophenyl)ethylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics:
MS(ES⁺) m/e 514 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*6) δ 9.52 (br, 1H), 7.67 (br, 1H), 7.49 (m, 3H), 7.24 (m, 5H), 6.35 (br, 1H), 4.90 (m, 1H), 4.69 (m, 1H), 3.14 (m, 1H), 2.88 (m, 1H), 2.71 (m, 8H), 2.08 (m, 2H), 1.92 (m, 3H), 1.63 (m, 3H), 1.29 (m, 3H).

Compound 5, 4-[[3-(2,5-Dichlorobenzylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 492 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 7.3 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.18 (m, 2H), 7.12 (m, 2H), 6.83 (br, 2H), 4.54 (m, 1H), 4.36 (d, J = 3.9 Hz, 2H), 3.24 (m, 2H), 3.09 (m, 1H), 2.74 (m, 5H), 2.43 (m, 1H), 2.12 (m, 2H), 2.01-1.83 (m, 4H), 1.77 (m, 1H), 1.65 (m, 2H).

Compound 6: MS(ES⁺) m/e 404 [M+H]⁺

Compound 7: MS(ES⁺) m/e 420 [M+H]⁺

Compound 8: MS(ES⁺) m/e 386 [M+H]⁺

Compound 9, N-(2-Chlorobenzylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-butyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 436 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (m, 1H), 7.35 (m, 1H), 7.22 (m, 8H), 4.42 (d, J = 6.1 Hz, 2H), 3.88 (m, 1H), 3.16 (m, 2H), 2.45 (m, 4H), 1.42 (m, 2H), 1.25 (m, 7H), 0.87 (t, J = 7.3 Hz, 3H).

Compound 10, 4-[[3-(2-Chlorobenzylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 450 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.42 (m, 1H), 7.35 (m, 2H),
5 7.29 (m, 1H), 7.16 (m, 3H), 7.07 (t, J = 8.5 Hz, 2H), 6.52 (m, 1H), 4.44 (d, J = 5.4 Hz, 2H), 4.24 (q, J = 6.8 Hz, 1H), 3.22 (m, 2H), 2.98 (m, 1H), 2.82-2.74 (m, 3H), 2.35 (m, 2H), 1.84 (m, 4H), 1.55 (d, J = 6.8 Hz, 3H).

Compound 11, 4-[[3-(2-Chlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to
10 that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 488 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (m, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.30 (m, 3H), 7.16 (m, 3H), 6.43 (br, 1H), 4.44 (d, J = 4.6 Hz, 2H), 4.19 (q, J = 6.8 Hz, 1H), 3.21 (m, 2H), 2.95 (m, 1H), 2.82-2.72 (m, 3H), 2.34 (m, 2H), 1.83 (m, 4H), 1.53 (d, J = 6.8 Hz, 3H).

Compound 12, 4-[[3-(2,4-Dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 522 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (m, 3H), 7.31 (m, 3H),
15 7.16 (m, 1H), 6.69 (br, 1H), 4.39 (d, J = 4.6 Hz, 2H), 4.22 (q, J = 6.8 Hz, 1H),
20 3.21 (m, 2H), 2.96 (m, 1H), 2.87-2.75 (m, 3H), 2.36 (m, 2H), 1.84 (m, 4H), 1.56 (d, J = 6.8 Hz, 3H).

Compound 14, 4-[[3-(3-Methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺)
25 m/e 468 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (m, 2H), 7.28 (m, 2H), 7.11 (m, 3H), 7.00 (d, J = 7.1 Hz, 1H), 6.31 (br, 1H), 4.31 (bs, 2H), 4.15 (q, J = 6.8 Hz, 1H), 3.20 (m, 1H), 2.91 (m, 1H), 2.82-2.67 (m, 3H), 2.33 (m, 2H), 2.29 (s, 3H), 1.84-1.68 (m, 4H), 1.51 (d, J = 6.8 Hz, 3H).

Compound 15, 4-[[3-(4-Methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 468 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 6.30 (br, 1H), 4.30 (bs, 2H), 4.15 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.91 (m, 1H), 2.82-2.66 (m, 3H), 2.32 (m, 2H), 2.28 (s, 3H), 1.84-1.68 (m, 4H), 1.51 (d, J = 6.8 Hz, 3H).

Compound 16, 4-[[3-(3,4-Dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 522 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 6.89 (br, 1H), 4.30 (bs, 2H), 4.23 (q, J = 6.8 Hz, 1H), 3.21 (m, 2H), 2.96 (m, 1H), 2.88-2.76 (m, 3H), 2.36 (m, 2H), 1.82 (m, 4H), 1.56 (d, J = 6.8 Hz, 3H).

Compound 17, 4-[[3-(4-Methoxybenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 484 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.26 (br, 1H), 4.27 (bs, 2H), 4.16 (q, J = 6.8 Hz, 1H), 3.75 (s, 3H), 3.19 (m, 2H), 2.91 (m, 1H), 2.83-2.67 (m, 3H), 2.32 (m, 2H), 1.84-1.68 (m, 4H), 1.52 (d, J = 6.8 Hz, 3H).

Compound 18, 4-[[3-(4-Bromobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 532 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (m, 4H), 7.30 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.60 (br, 1H), 4.29 (bs, 2H), 4.21 (q, J = 6.8

6.8 Hz, 1H), 4.40 (d, J = 4.1 Hz, 2H), 3.25 (m, 2H), 3.11 (m, 1H), 2.88 (m, 3H), 2.45 (m, 1H), 2.32 (m, 1H), 1.88 (m, 3H), 1.75 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H).

Compound 33, 4-[[3-(2,4-Dichlorobenzylureido)propyl](1,2,3,4-tetrahydro-
5 1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 492 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, J = 7.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.20 (m, 3H), 7.13 (m, 2H), 6.89 (br, 1H), 4.57 (m, 1H), 4.38 (d, J = 3.4 Hz, 2H), 3.26 (m, 2H), 3.13 (m, 1H), 2.87 (m, 1H), 2.76 (m, 4H), 2.43
10 (dd, J = 16.6, 5.6 Hz, 1H), 2.13 (m, 2H), 1.94 (m, 4H), 1.75 (m, 1H), 1.66 (m, 2H).

Compound 34, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1R)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺)
15 m/e 500 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 3H), 7.30 (m, 3H), 7.16 (dd, J = 8.3, 2.0 Hz, 1H), 6.83 (br, 1H), 4.39 (d, J = 5.1 Hz, 2H), 4.20 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.95 (m, 1H), 2.78 (m, 3H), 2.35 (m, 2H), 1.80 (m, 4H), 1.54 (d, J = 6.8 Hz, 3H).

Compound 35, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1S)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺)
20 m/e 500 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 3H), 7.30 (m, 3H), 7.16 (dd, J = 8.3, 2.2 Hz, 1H), 6.84 (br, 1H), 4.39 (d, J = 5.1 Hz, 2H), 4.19 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.95 (m, 1H), 2.78 (m, 3H), 2.36 (m, 2H), 1.80
25 (m, 4H), 1.53 (d, J = 6.8 Hz, 3H).

Compound 36, 4-[[3-(2,4-Dichlorobenzylureido)propyl](7-methoxy-1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 522 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, J = 8.3 Hz,

1H), 7.28 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.3, 2.2 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.82 (br, 2H), 6.79 (dd, J = 8.5, 2.4 Hz, 1H), 4.52 (t, J = 7.3 Hz, 1H), 4.37 (d, J = 5.1 Hz, 2H), 3.71 (s, 3H), 3.26 (m, 2H), 3.15 (m, 1H), 2.85 (m, 1H), 2.75 (m, 2H), 2.68 (m, 2H), 2.46 (m, 1H), 2.12 (m, 2H), 1.95 (m, 4H), 1.68 (m, 3H).

Compound 37, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1S)-1-(4-methylphenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 502 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.06 (br, 1H), 4.40 (d, J = 5.4 Hz, 2H), 4.25 (q, J = 6.8 Hz, 1H), 3.24 (m, 2H), 3.07 (m, 1H), 2.88 (m, 2H), 2.80 (m, 1H), 2.37 (m, 2H), 2.35 (s, 3H), 1.88 (m, 3H), 1.75 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H).

Compound 38, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1S)-1-(4-methoxyphenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 518 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.3 Hz, 1H), 7.28 (m, 3H), 7.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.02 (br, 1H), 6.90 (d, J = 8.8 Hz, 2H), 4.40 (d, J = 5.4 Hz, 2H), 4.27 (m, 1H), 3.80 (s, 3H), 3.24 (m, 2H), 3.05 (m, 1H), 2.87 (m, 2H), 2.82 (m, 1H), 2.35 (m, 2H), 1.89 (m, 3H), 1.77 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H).

Compound 39, 4-[[3-(2,4-Dichlorobenzylureido)propyl](1-indanyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 478 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.3 Hz, 1H), 7.30 (m, 3H), 7.22 (m, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.01 (br, 1H), 6.93 (m, 1H), 4.88 (m, 1H), 4.40 (d, J = 5.6 Hz, 2H), 3.26 (m, 2H), 3.02 (m, 3H), 2.77 (m, 3H), 2.53 (dd, J = 16.8, 6.8 Hz, 1H), 2.35 (m, 1H), 2.21 (m, 1H), 2.13 (m, 1H), 1.93 (m, 3H), 1.71 (m, 1H).

Compound 40, 4-[[3-(2,4-Dichlorobenzylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 484 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.36 (m, 3H), 7.31 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.3, 2.0 Hz, 1H), 7.08 (t, J = 8.5 Hz, 2H), 6.80 (br, 1H), 4.39 (d, J = 5.4 Hz, 2H), 4.26 (q, J = 6.8 Hz, 1H), 3.22 (m, 2H), 2.99 (m, 1H), 2.81 (m, 3H), 2.35 (m, 2H), 1.83 (m, 4H), 1.57 (d, J = 6.8 Hz, 3H).

Compound 41, N-(2,4-Dichlorobenzylcarbonyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-butyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 470 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 2H), 7.27 (bs, 4H), 7.19 (m, 1H), 4.85 (br, 1H), 4.36 (d, J = 6.1 Hz, 2H), 3.88 (q, J = 6.8 Hz, 1H), 3.13 (m, 2H), 2.45 (m, 4H), 1.58 (m, 2H), 1.43 (m, 2H), 1.32 (d, J = 6.6 Hz, 3H), 1.26 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H).

Compound 42, 4-[[4-(2,4-Dichlorobenzylureido)butyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 536 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.36 (m, 3H), 7.30 (m, 3H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 6.72 (m, 1H), 6.45 (br, 1H), 4.38 (d, J = 5.1 Hz, 2H), 4.23 (q, J = 6.8 Hz, 1H), 3.17 (m, 2H), 2.84 (m, 2H), 2.73 (m, 1H), 2.60 (m, 1H), 2.39 (m, 2H), 1.80 (m, 2H), 1.67 (m, 2H), 1.54 (d, J = 7.1 Hz, 3H), 1.45 (m, 2H).

Compound 43, 4-[[5-(2,4-Dichlorobenzylureido)pentyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES⁺) m/e 550 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (m, 3H), 7.33 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 2.2 Hz, 1H), 7.16 (m, 1H), 6.67 (br, 1H), 6.35 (br, 1H), 4.39 (d, J = 5.4 Hz, 2H), 4.29 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.83 (m, 2H),

2.68 (m, 2H), 2.42 (m, 1H), 2.35 (m, 1H), 1.81 (m, 2H), 1.67 (m, 2H), 1.58 (d, J = 7.1 Hz, 3H), 1.46 (m, 4H).

Compounds 6-8 can be obtained in an analogous manner to that of Compound 13.

5 Example 3. Synthesis of Methyl 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate (Compound 27)

The following synthesis is depicted in Scheme 3.

To a mixture of 50% KOH (6 ml) and ether (6 ml) was added 1-methyl-3-nitro-1-nitrosoguamidine (0.5 g, 3.4 mmol) at 0 °C. After standing at 0 °C for 5
10 min, the organic layer was transferred to another Erlenmeyer flask at 0 °C, and KOH pellets (0.5 g) was added. After standing at 0 °C for 5 min, the supernatant (1 ml) was added to a solution of 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 13, 16 mg, 0.04 mmol) in CH₂Cl₂ (2 ml) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was
15 concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford Methyl 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate (16 mg, 90%): MS(ES⁺) m/e 482 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (m, 5H), 7.16 (m, 3H), 4.81 (br, 1H), 4.59 (br, 1H), 4.33 (d, J = 5.4 Hz, 2H), 3.86 (q, J =
20 6.8 Hz, 1H), 3.59 (s, 3H), 3.18 (m, 2H), 2.48 (m, 3H), 2.32 (s, 3H), 2.29 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.62 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H).

Compound 3, Methyl 4-[[3-[1-(4-Bromophenyl)ethylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺)
25 m/e 530 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56 (d, J = 7.3 Hz, 1H), 7.48 (dd, J = 8.3, 1.2 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.06 (m, 3H), 6.26 (m, 1H), 5.71 (m, 1H), 4.67 (m, 1H), 3.85 (m, 1H), 3.54 (s, 3H), 3.00 (m, 1H), 2.91 (m, 1H), 2.67 (m, 2H), 2.34 (m, 6H), 1.92 (m, 2H), 1.64 (m, 3H), 1.49 (m, 3H), 1.27 (d, J = 7.1 Hz, 3H).

Compound 19, Methyl 4-[[3-(2-chlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 480 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, J = 7.3, 2.0 Hz, 1H), 7.34 (dd, J = 7.3, 2.0 Hz, 1H), 7.26 (m, 3H), 7.21 (m, 3H), 4.95 (br, 1H), 4.43 (d, J = 6.1 Hz, 2H), 3.87 (m, 1H), 3.63 (s, 3H), 3.18 (m, 2H), 2.48 (m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 1.74 (m, 2H), 1.62 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H).

Compound 20, Methyl 4-[[3-(3-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 460 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (s, 1H), 7.20 (m, 3H), 7.07 (m, 4H), 4.75 (br, 1H), 4.30 (d, J = 5.6 Hz, 2H), 3.85 (m, 1H), 3.61 (s, 3H), 3.17 (m, 2H), 2.47 (m, 3H), 2.33 (s, 3H), 2.31 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.61 (m, 2H), 1.29 (d, J = 6.6 Hz, 3H).

Compound 21, Methyl 4-[[3-(4-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 460 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (m, 4H), 7.17 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 4.73 (br, 1H), 4.28 (d, J = 5.6 Hz, 2H), 3.85 (q, J = 6.8 Hz, 1H), 3.61 (s, 3H), 3.17 (m, 2H), 2.46 (m, 3H), 2.34 (m, 1H), 2.32 (s, 3H), 2.25 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H).

Compound 22, Methyl 4-[[3-(3,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 513 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (m, 2H), 7.26 (m, 4H), 7.12 (m, 1H), 5.03 (br, 1H), 4.29 (d, J = 6.1 Hz, 2H), 3.89 (m, 1H), 3.63 (s, 3H), 3.18 (m, 2H), 2.49 (m, 3H), 2.35 (m, 1H), 2.27 (m, 2H), 1.75 (m, 2H), 1.62 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H).

Compound 23, Methyl 4-[[3-(4-methoxybenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 476 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (m, 4H), 7.21 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.75 (br, 1H), 4.26 (d, J = 5.6 Hz, 2H), 3.86 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.16 (m, 2H), 2.47 (m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.60 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H).

Compound 24, Methyl 4-[[3-(4-bromobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 525 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 8.3 Hz, 2H), 7.26 (m, 4H), 7.17 (d, J = 8.3 Hz, 2H), 4.85 (br, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.89 (m, 1H), 3.62 (s, 3H), 3.19 (m, 2H), 2.50 (m, 3H), 2.36 (m, 1H), 2.26 (m, 2H), 1.75 (m, 2H), 1.63 (m, 2H), 1.31 (d, J = 6.6 Hz, 3H).

Compound 25, Methyl 4-[[3-(benzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 446 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (m, 3H), 7.25 (m, 6H), 4.82 (br, 1H), 4.34 (d, J = 5.9 Hz, 2H), 3.86 (m, 1H), 3.61 (s, 3H), 3.18 (m, 2H), 2.48 (m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.61 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H).

Compound 26, Methyl 4-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 536 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.36 (m, 2H), 7.26 (m, 4H), 7.20 (m, 1H), 4.95 (br, 1H), 4.39 (d, J = 6.1 Hz, 2H), 3.88 (m, 1H), 3.64 (s, 3H), 3.17 (m, 2H), 2.48 (m, 3H), 2.35 (m, 1H), 2.26 (m, 2H), 1.75 (m, 2H), 1.61 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H).

Compound 29, Methyl 4-[[3-(2-chlorobenzylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES⁺) m/e 486 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (m, 1H), 7.33 (m, 1H), 7.26 (m, 2H), 7.20 (m, 2H), 6.97 (m, 2H), 5.04 (br, 1H), 4.42 (d, J = 6.1 Hz, 2H), 3.85 (q, J = 6.8 Hz, 1H), 3.62 (s, 3H), 3.16 (m, 2H), 2.45 (m, 3H), 2.32 (m, 1H), 2.24 (m, 2H), 1.72 (m, 2H), 1.59 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H).

Example 4. Synthesis of 5-[[3-(2,4-Dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoic acid (Compound 47)

The following synthesis is depicted in Scheme 4.

To a solution of Methyl 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoate (Compound 44, 50 mg, 0.095 mmol) in 10% water/methanol (2 ml) was added lithium hydroxide monohydrate (30 mg, 0.71 mmol). After stirring at RT for 16 h, the reaction mixture was concentrated under vacuum to dryness. After adding 1N-HCl, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and the plate was developed with 17% methanol/chloroform to afford 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoic acid (17 mg, 35%): MS(ES⁺) m/e 514 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (bs, 4H), 7.29 (m, 2H), 7.15 (m, 1H), 6.32 (br, 1H), 4.34 (bs, 2H), 4.06 (q, J = 6.8 Hz, 1H), 3.14 (m, 2H), 2.71 (m, 1H), 2.64 (m, 2H), 2.52 (m, 1H), 2.22 (m, 2H), 1.73 (m, 2H), 1.52 (m, 2H), 1.44 (d, J = 6.8 Hz, 3H).

Example 5. Synthesis of N-(3,4-Dichlorophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane (Compound 53)

The following synthesis is depicted in Scheme 5.

Step 1: To a mixture of 2-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in CH₃CN (50 ml) was added N-(3-

bromopropyl)phthalimide (3.0 g, 11 mmol). The mixture was refluxed under stirring for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford N-[3-[2-(4-

- 5 chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 67%): MS(FD) m/e 343 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.74 (d, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.84 (m, 2H).

Step 2: To a mixture of N-[3-[2-(4-

- 10 chlorophenyl)ethylamino]propyl]phthalimide (244 mg, 0.712 mmol) and potassium carbonate (148 mg, 1.07 mmol) in CH₃CN (4 ml) was added 1-bromo-2-(2-methoxyethoxy)ethane (195 mg, 1.07 mmol). The mixture was refluxed under stirring for 13 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and the plate was
- 15 developed with 3% methanol/chloroform to afford N-[3-[[2-(4-chlorophenyl)ethyl] [2-(2-methoxyethoxy)ethyl]amino]propyl]phthalimide (158 mg, 50%): MS(ES⁺) m/e 445 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.70 (m, 2H), 3.58 (m, 2H), 3.53 (m, 4H), 3.37 (s, 3H), 2.71 (m, 6H), 2.62 (m, 2H), 1.83 (m, 2H).

- 20 Step 3: To a solution of N-[3-[[2-(4-chlorophenyl)ethyl] [2-(2-methoxyethoxy)ethyl]amino]propyl]phthalimide (70 mg, 0.16 mmol) in ethanol (3 ml) was added hydrazine monohydrate (53 μl, 1.1 mmol). The solution was stirred at RT for 21 h, and then filtered. The filtrate was concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, washed
- 25 with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. After adding chloroform (2 ml) to the residue, 3,4-dichlorophenyl isocyanate (44 mg, 0.24 mmol) was added, and the mixture was stirred at RT for 1.5 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica

gel and then developed with 5% methanol/chloroform to afford N-(3,4-dichlorophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane (50 mg, 63%): MS(ES⁺) m/e 502 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J = 2.4 Hz, 1H), 7.61 (br, 1H),
5 7.30 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (m, 3H), 7.11 (d, J = 8.3 Hz, 2H), 6.35 (br, 1H), 3.63 (m, 6H), 3.36 (s, 3H), 3.27 (m, 2H), 2.75 (m, 6H), 2.70 (m, 2H), 1.71 (m, 2H).

Compound 48, N-(4-Cyanophenylcarbamoyl)-N'-[2-(2,4-dichlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be
10 obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 493 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.19 (br, 1H), 7.53 (m, 5H), 7.34 (d, J = 6.3 Hz, 1H), 7.15 (s, 1H), 6.42 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.28 (m, 2H), 2.86 (m, 2H), 2.76 (m, 4H), 2.67 (m, 2H), 1.71 (m, 2H).

15 Compound 49, N-(4-Methoxyphenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 464 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, J = 9.0 Hz, 2H), 7.18 (m, 3H), 7.05 (m, 1H), 6.95 (br, 1H), 6.81 (d, J
20 = 9.0 Hz, 2H), 5.94 (br, 1H), 3.76 (s, 3H), 3.63 (m, 2H), 3.59 (m, 4H), 3.35 (s, 3H), 3.26 (m, 2H), 2.69 (m, 6H), 2.61 (m, 2H), 1.66 (m, 2H).

Compound 50, N-(4-Cyanophenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following
25 characteristics: MS(ES⁺) m/e 459 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (br, 1H), 7.55 (m, 2H), 7.50 (m, 2H), 7.17 (m, 3H), 7.05 (m, 1H), 6.42 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.24 (m, 2H), 2.71 (m, 6H), 2.62 (t, J = 5.9 Hz, 2H), 1.69 (m, 2H).

Compound 51, N-(3,4-Dichlorophenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 502 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃)
5 δ 7.64 (d, J = 2.4 Hz, 1H), 7.56 (br, 1H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.18 (m, 3H), 7.06 (m, 1H), 6.35 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.24 (m, 2H), 2.71 (m, 6H), 2.63 (t, J = 5.9 Hz, 2H), 1.68 (m, 2H).

Compound 52, N-(3,4-Dichlorophenylcarbamoyl)-N'-[2-(2,4-dichlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be
10 obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 536 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃)
 δ 7.65 (d, J = 2.4 Hz, 1H), 7.36 (s, 1H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 6.35 (br, 1H), 3.66 (m, 6H), 3.36 (s, 3H), 3.30 (m, 2H), 2.86 (m, 2H), 2.71 (m, 6H), 1.72 (m, 2H).

Compound 54, N-(4-Cyanophenylcarbamoyl)-N'-[2-(3,4-dichlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be
15 obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 493 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃)
 δ 7.94 (br, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.33 (d, J =
20 8.0 Hz, 1H), 7.27 (m, 1H), 7.01 (dd, J = 8.3, 2.0 Hz, 1H), 6.40 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.26 (m, 2H), 2.73 (m, 6H), 2.64 (t, J = 5.9 Hz, 2H), 1.71 (m, 2H).

Compound 55, N-(Phenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner
25 to that described for compound 53 and contains the following characteristics:
MS(ES⁺) m/e 434 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (dd, J = 8.5, 1.0 Hz, 2H), 7.28 (br, 1H), 7.23 (m, 2H), 7.17 (m, 3H), 7.05 (m, 1H), 6.95 (m, 1H), 6.10 (br, 1H), 3.63 (m, 6H), 3.36 (s, 3H), 3.26 (m, 2H), 2.71 (m, 6H), 2.61 (t, J = 6.1 Hz, 2H), 1.66 (m, 2H).

Compound 56, N-(3,4-Dichlorophenylcarbamoyl)-N'-(2-phenylethyl)-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 468 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 2.4 Hz, 1H), 7.49 (br, 1H), 7.30 (m, 1H), 7.25 (m, 3H), 7.18 (m, 3H), 6.38 (br, 1H), 3.63 (m, 6H), 3.35 (s, 3H), 3.26 (m, 2H), 2.74 (m, 4H), 2.70 (m, 2H), 2.63 (m, 2H), 1.68 (m, 2H).

Compound 57, N-(Phenylcarbamoyl)-N'-[2-(3-methoxyphenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁺) m/e 430 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (dd, J = 8.5, 1.0 Hz, 2H), 7.21 (m, 4H), 6.95 (t, J = 7.3 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.73 (m, 2H), 6.18 (br, 1H), 3.77 (s, 3H), 3.62 (m, 6H), 3.35 (s, 3H), 3.29 (t, J = 5.6 Hz, 2H), 2.73 (bs, 4H), 2.70 (m, 2H), 2.63 (m, 2H), 1.68 (m, 2H).

Compound 58, N-(Phenylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁻) m/e 432 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (m, 1H), 7.41 (m, 2H), 7.33 (m, 2H), 7.26 (m, 4H), 6.95 (t, J = 6.3 Hz, 1H), 6.17 (br, 1H), 4.00 (q, J = 6.8 Hz, 1H), 3.69-3.45 (m, 7H), 3.19 (m, 1H), 2.60 (m, 3H), 2.55 (m, 1H), 1.67 (m, 2H), 1.32 (d, J = 6.8 Hz, 3H).

Compound 59, N-(4-Bromophenylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES⁻) m/e 510 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (br, 1H), 7.33 (m, 4H), 7.27 (m, 4H), 6.33 (br, 1H), 4.03 (m, 1H), 3.75-3.48 (m, 7H), 3.37 (s, 3H), 3.16 (m, 1H), 2.62 (m, 3H), 2.55 (m, 1H), 1.68 (m, 2H), 1.33 (d, J = 6.8 Hz, 3H).

Compound 60, N-(Phenylcarbamoyl)-N'-[2-(2-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics:

MS(ES⁺) m/e 456 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, J = 7.6 Hz, 2H), 7.33 (m, 1H), 7.29 (br, 1H), 7.22 (m, 3H), 7.15 (m, 2H), 6.94 (m, 1H), 6.25 (br, 1H), 3.66 (m, 6H), 3.36 (s, 3H), 3.30 (m, 2H), 2.88 (m, 2H), 2.75 (m, 4H), 2.67 (m, 2H), 1.70 (m, 2H).

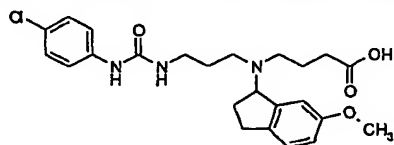
Compound 61, N-(Phenylcarbamoyl)-N'-[2-(4-bromophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics:

MS(ES⁺) m/e 500 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (m, 4H), 7.29 (br, 1H), 7.23 (m, 2H), 7.05 (d, J = 8.3 Hz, 2H), 6.95 (m, 1H), 3.61 (m, 6H), 3.36 (s, 3H), 3.27 (t, J = 5.6 Hz, 2H), 2.69 (m, 6H), 2.62 (m, 2H), 1.68 (m, 2H).

Compound 62, N-(Phenylcarbamoyl)-N'-[2-(4-fluorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics:

MS(ES⁺) m/e 440 [M+Na]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (dd, J = 8.5, 1.0 Hz, 2H), 7.28 (br, 1H), 7.23 (m, 2H), 7.13 (m, 2H), 6.95 (m, 3H), 3.63 (m, 6H), 3.37 (s, 3H), 3.27 (m, 2H), 2.70 (m, 6H), 2.63 (m, 2H), 1.68 (m, 2H).

Example 6. Synthesis of 4-[[3-[(4-Chloroanilino)carbonylamino]propyl](6-methoxy-1-indanyl)amino]butanoic acid (Compound 63):



The following synthesis is depicted in Scheme 6.

Step 1: To a solution of 6-methoxy-1-indanone (5.0 g, 30 mmol) in EtOH (20 ml) was added sodium borohydride (3.5g, 93 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 h. The solution was concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, dried over sodium

sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 30% ethyl acetate/hexane) to afford 6-methoxy-1-indanol (5.0 g, 99%): ^1H NMR (400 MHz, CDCl_3) δ 7.03 (d, $J = 8.0$ Hz, 1H), 6.84 (s, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 5.07 (t, $J = 6.0$ Hz, 1H), 2.86 (m, 1H), 2.64 (m, 1H), 2.39 (m, 1H), 1.82 (m, 1H).

Step 2: To a solution of 6-methoxy-1-indanol (4.6 g, 28 mmol) in toluene (50 ml) were added iminodicarboxylic acid di-*tert*-butyl ester (9.2 g, 42 mmol) and tri-*n*-butylphosphine (8.6 g, 42 mmol), and the mixture was cooled to 0 °C. After adding 1,1'-(azodicarbonyl)dipiperidine, the solution was stirred at RT for 3 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 4% ethyl acetate/hexane) to afford *tert*-butyl [(*tert*-butoxycarbonyl)(6-methoxy-1-indanyl)amino]methanoate (8.5 g, 83%): MS(ES^+) m/e 386 [$\text{M} + \text{Na}$] $^+$; ^1H NMR (400 MHz, CDCl_3) δ 7.00 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.64 (s, 3H), 5.70 (t, $J = 8.4$ Hz, 1H), 3.68 (s, 3H), 2.90 (m, 1H), 2.72 (m, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 1.29 (m, 18H).

Step 3: *tert*-Butyl[(*tert*-butoxycarbonyl)(6-methoxy-1-indanyl)amino]methanoate (8.5 g, 23 mmol) in 40% TFA/ CH_2Cl_2 was stirred at RT for 2 h. After neutralized with 50% NaOH aq. the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. Concentrating under vacuum gave 1-amino-6-methoxyindan (1.9 g, 50%) which was used in the next step without further purification.

Step 4: To a mixture of 1-amino-6-methoxyindan (1.9 g, 12 mmol) and potassium carbonate (5.0 g, 36 mmol) in CH_3CN (50 ml) was added *N*-(3-Bromopropyl)phthalimide (3.9 g, 14 mmol). The mixture was refluxed under stirring for 18 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford 2-[3-[(6-methoxy-1-indanyl)amino]propyl]-1,3-isoindolinedione (2.5 g, 60%): MS(ES^+) m/e 351 [$\text{M} + \text{H}$] $^+$; ^1H NMR (400 MHz,

CDCl₃) δ 7.75 (m, 2H), 7.63 (m, 2H), 7.05 (d, J = 4.0 Hz, 1H), 6.81 (s, 1H), 6.65 (d, J = 4.0 Hz, 2H), 4.09 (t, J = 6.8 Hz, 1H), 3.72 (m, 5H), 2.72-2.52 (m, 4H), 2.29 (m, 1H), 1.84-1.71 (m, 3H).

Step 5: To a solution of 2-[3-[(6-methoxy-1-indanyl)amino]propyl]-1,3-
5 isoindolinedione (2.4 g, 7.0 mmol) in 20% EtOH/DMF (30 ml) were added succinic semialdehyde (15 wt. % solution in water, 12 ml, 17 mmol) and BAP (3.6 ml, 35 mmol), and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the
10 residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[3-(1,3-dioxo-2-isoindolyl)propyl](6-methoxy-1-indanyl)amino]butanoic acid (1.3 g, 43%): MS(ES⁺) m/e 437 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (m, 2H), 7.71 (m, 2H), 7.05 (m, 2H), 6.75 (d, J = 8.4 Hz, 1H), 4.68 (t, J = 6.8 Hz 1H), 3.73-3.63 (m, 5H), 2.91-2.74 (m, 3H), 2.62-2.50 (m, 4H), 2.29-2.15
15 (m, 2H), 2.14-2.01 (m, 3H), 1.96-1.87 (m, 1H).

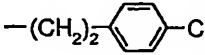
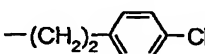
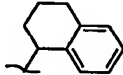
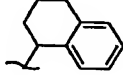
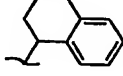
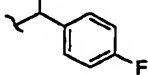
Step 6: To a solution of 4-[[3-(1,3-dioxo-2-isoindolyl)propyl](6-methoxy-1-indanyl)amino]butanoic acid (1.3 g, 3.3 mmol) in EtOH (50 ml) was added hydrazine monohydrate (0.35 ml, 8.5 mmol), and the mixture was stirred at RT for 6 h. After adding chloroform (50 ml) and MeOH (25 ml), the reaction mixture was
20 filtered, and the filtrate was concentrated under vacuum to dryness. After adding DMF (30 ml) to the residue, 4-chlorophenyl isocyanate (1.5 g, 9.7 mmol) was added, and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was chromatographed on
25 silica gel (eluting with 17% methanol/chloroform) to afford 4-[[3-[(4-chloroanilino)carbonylamino]propyl](6-methoxy-1-indanyl)amino]butanoic acid (520 mg, 34%): MS(ES⁻) m/e 458 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃) δ 9.20(bs, 1H), 7.43-7.12 (m, 6H), 7.87 (m, 1H), 4.90 (t, J = 6.8 Hz, 1H), 4.69 (s, 3H), 3.38-2.84 (m, 8H), 2.55-2.01(m, 7H), 1.80 (m, 1H).

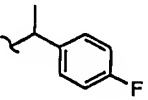
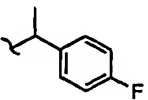
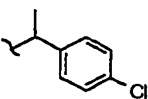
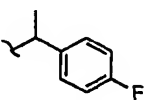
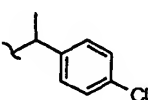
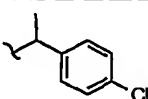
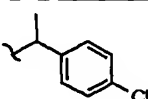
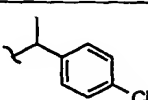
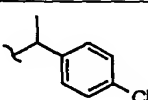
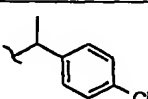
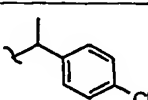
Abbreviations:

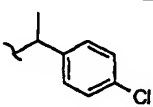
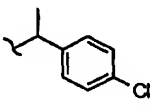
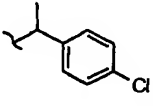
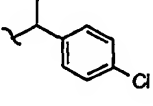
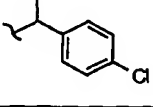
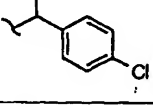
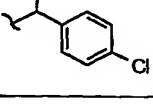
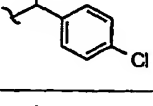
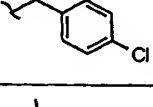
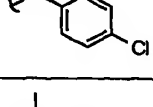
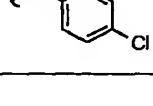
EtOH	ethanol
MeOH	methanol
DMF	N,N-dimethylformamide
BAP	borane and pyridine
TFA	trifluoroacetic acid

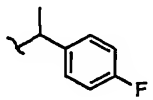
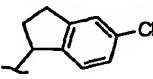
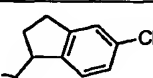
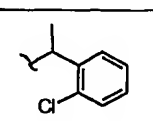
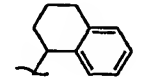
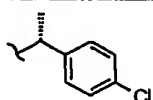
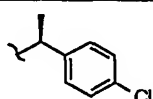
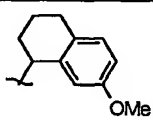
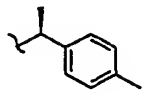
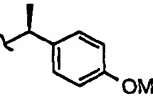
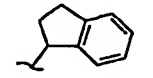
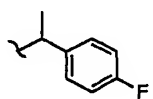
Tables 1a, 1b, and 1c list a variety of compounds that can be synthesized by using one of the methods described above.

Table 1A

CPD No.	Ar	R11,R12	m	R1	R2	Mass Spec. m/e		
1	Phenyl	H,H	3		ethyl	ES ⁻	408	[M-H] ⁻
2	Phenyl	H,H	2		ethyl	ES ⁻	394	[M-H] ⁻
3	4-bromophenyl	Me,H	3		-(CH ₂) ₃ CO ₂ Me	ES ⁺	530	[M+H] ⁺
4	4-bromophenyl	Me,H	3		-(CH ₂) ₃ CO ₂ H	ES ⁻	514	[M-H] ⁻
5	2,5-dichlorophenyl	H,H	3		-(CH ₂) ₃ CO ₂ H	ES ⁺	492	[M+H] ⁺
6	4-fluorophenyl	H,H	3		-(CH ₂) ₃ CH ₃	ES ⁺	404	[M+H] ⁺

7	2-chlorophenyl	H,H	3		$-(CH_2)_3CH_3$	ES ⁺	420	M+H] ⁺
8	phenyl	H,H	3		$-(CH_2)_3CH_3$	ES ⁺	386	M+H] ⁺
9	2-chlorophenyl	H,H	3		$-(CH_2)_3CH_3$	ES ⁺	436	M+H] ⁺
10	2-chlorophenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	450	M+H] ⁺
11	2-chlorophenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	488	M+Na]
12	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	522	M+Na]
13	2-methylphenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	468	M+Na]
14	3-methylphenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	468	M+Na]
15	4-methylphenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	468	M+Na]
16	3,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	522	M+Na]
17	4- methoxyphenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	484	M+Na]

18	4-bromophenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	532	M+Na]
19	2-chlorophenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	480	M+H] ⁺
20	3-methylphenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	460	M+H] ⁺
21	4-methylphenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	460	M+H] ⁺
22	3,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	513	M+H] ⁺
23	4- methoxyphenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	476	M+H] ⁺
24	4-bromophenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	525	M+H] ⁺
25	Phenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	446	M+Na]
26	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	536	M+Na]
27	2-methylphenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES ⁺	482	M+Na]
28	Phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES ⁺	454	M+Na]

29	2-chlorophenyl	H,H	3		$-(CH_2)_3CO_2Me$	ES^+	486	$M+Na]$
30	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	512	$M+H]^+$
31	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	500	$M+H]^+$
32	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	522	$M+Na]$
33	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	492	$M+H]^+$
34	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	500	$M+H]^+$
35	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	500	$M+H]^+$
36	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	522	$M+H]^+$
37	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	502	$M+Na]$
38	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	518	$M+Na]$
39	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	478	$M+H]^+$
40	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2H$	ES^+	484	$M+H]^+$

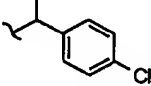
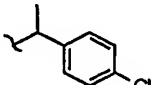
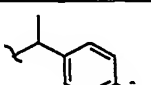
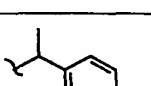
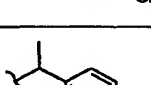
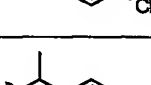
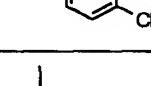
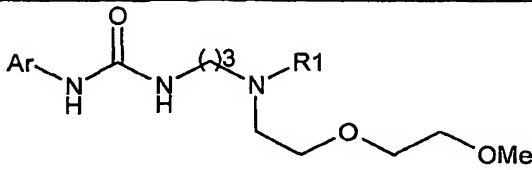
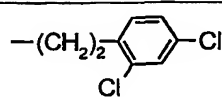
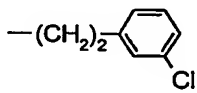
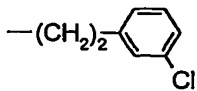
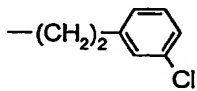
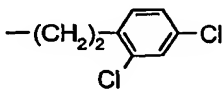
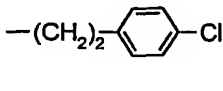
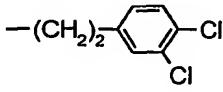
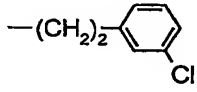
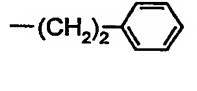
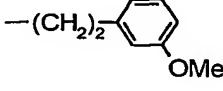
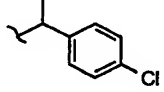
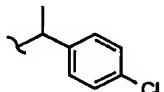
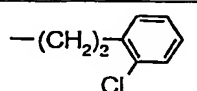
41	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CH_3$	ES ⁺	470	$[M+H]^+$
42	2,4-dichloro phenyl	H,H	4		$-(CH_2)_3CO_2H$	ES ⁺	536	$[M+Na]^+$
43	2,4-dichloro phenyl	H,H	5		$-(CH_2)_3CO_2H$	ES ⁺	550	$[M+Na]^+$
44	2,4-dichloro phenyl	H,H	3		$-(CH_2)_4CO_2Me$	ES ⁺	550	$[M+Na]^+$
45	2,4-dichloro phenyl	H,H	3		$-(CH_2)_3CO_2Et$	ES ⁺	578	$[M+Na]^+$
46	2,4-dichloro phenyl	H,H	3		ethyl	ES ⁺	442	$[M+H]^+$
47	2,4-dichloro phenyl	H,H	3		$-(CH_2)_4CO_2H$	ES ⁺	514	$[M+H]^+$

Table 1B

					
CPD No.	Ar	R1	Mass Spec. m/e		
48	4-cyanophenyl		ES ⁺	493	$[M+H]^+$

49	4-methoxyphenyl		ES ⁺	464	[M+H] ⁺
50	4-cyanophenyl		ES ⁺	459	[M+H] ⁺
51	3,4-dichloro phenyl		ES ⁺	502	[M+H] ⁺
52	3,4-dichloro phenyl		ES ⁺	536	[M+H] ⁺
53	3,4-dichloro phenyl		ES ⁺	502	[M+H] ⁺
54	4-cyanophenyl		ES ⁺	493	[M+H] ⁺
55	phenyl		ES ⁺	434	[M+H] ⁺
56	3,4-dichloro phenyl		ES ⁺	468	[M+H] ⁺
57	phenyl		ES ⁺	430	[M+H] ⁺
58	phenyl		ES ⁻	432	[M-H] ⁻
59	4-bromophenyl		ES ⁻	510	[M-H] ⁻
60	phenyl		ES ⁺	456	[M+Na] ⁺

Example 7. Synthesis of 4-[[3-[2-[4-(Benzyloxy)-3-methoxyphenyl]acetylaminopropyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 87)

The following synthesis is depicted in Scheme 7.

5 Step 1: N-(3-Bromopropyl)phthalimide (4.1 g, 15 mmol) was added to a mixture of 1-(4-chlorophenyl)ethylamine (2.0 g, 13 mmol) and potassium carbonate (5.3 g, 39 mmol) in CH₃CN (50 ml). The mixture was refluxed under stirring for 18 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 1.5% methanol/chloroform) to afford N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (3.0 g, 68%):
10 MS(ES⁺) m/e 343 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (m, 2H), 7.72 (m, 2H), 7.23 (d, J = 8.0 Hz, 4H), 3.73 (m, 3H), 2.50 (m, 1H), 2.44 (m, 1H), 1.83 (m, 2H), 1.32 (d, J = 6.6 Hz, 3H).

Step 2: To a solution of N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (1.4 g, 4.1 mmol) in 20% EtOH/DMF (50 ml) were added succinic semialdehyde (15 wt. % solution in water, 5.0 ml, 8.2 mmol) and BAP (0.80 ml, 8.2 mmol), and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[3-(phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.32 g, 75%): MS(ES⁺) m/e 429 [M+H]⁺;
15 ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.75 (m, 2H), 7.26 (m, 4H), 4.05 (q, J = 6.8 Hz, 1H), 3.68 (m, 2H), 2.81 (m, 2H), 2.69 (m, 1H), 2.58 (m, 1H), 2.44 (t, J = 5.9 Hz, 2H), 2.01 (m, 2H), 1.82 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H).
20 25

Step 3: To a solution of 4-[[3-(phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (2.6 g, 5.3 mmol) in EtOH (10 ml) was added hydrazine monohydrate (0.7 ml, 13.3 mmol), and the mixture was stirred at RT for 6 h, and then filtered. The filtrate was concentrated under vacuum to

dryness. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave 4-[(3-aminopropyl)[1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.5 g, 85%) which was used in the next step without further purification.

- 5 Step 4: (4-Benzyloxy-3-methoxyphenyl)acetic acid (1.8g, 6.7 mmol) in 20% SOCl₂/CH₂Cl₂ was refluxed under stirring for 18h(see. Scheme 8). The reaction mixture was concentrated under vacuum to dryness. After adding 1,3-dioxane (10 ml) to the residue, 4-[(3-aminopropyl)[1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.5 g, 4.5 mmol) in DMF (30 ml) was added, and the mixture was stirred at RT
10 for 10 h. After adding water, the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was chromatographed on silica gel (eluting with 17% methanol/chloroform) to afford 4-[[3-[2-[4-(benzyloxy)-3-methoxyphenyl]acetyl]amino]propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid
15 (900mg, 36%) : MS(ES⁺) m/e 553 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.15 (m, 9H), 6.76 (m, 2H), 6.69 (m, 1H), 5.03 (s, 2H), 3.97 (q, J = 6.8 Hz, 1H), 3.79 (s, 3H), 3.36 (s, 2H), 3.13 (m, 2H), 2.56 (m, 2H), 2.44 (m, 2H), 1.71-1.51 (m, 4H), 1.33 (d, J = 6.8 Hz, 3H).

- Compound 90, 4-[[3-[2-[4-(benzyloxy)phenyl]acetyl]amino]propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES⁺) m/e 493 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.15 (m, 13H), 6.89 (br, 1H), 3.96 (q, J = 6.8 Hz, 3H), 3.46 (s, 2H), 3.15 (m, 2H), 2.57 (m, 2H), 2.44 (m, 2H), 2.24 (m, 2H), 1.69 (m, 2H), 1.58 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H).
20

- 25 Compound 109, 4-[[3-[2-[4-(benzyloxy)phenyl]acetyl]amino]propyl][(1S)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES⁺) m/e 524 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.16 (m, 11H),

6.93 (m, 2H), 5.03 (s, 2H), 4.06 (q, J=6.8Hz 1H), 3.46 (s, 2H), 3.21 (m, 2H),
2.70-2.47 (m, 4H), 2.39-2.23 (m, 2H), 1.81-1.62 (m, 4H), 1.44 (d, J=6.8Hz, 3H).

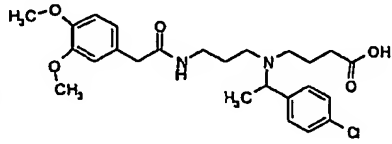
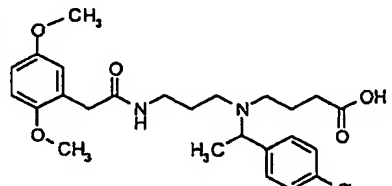
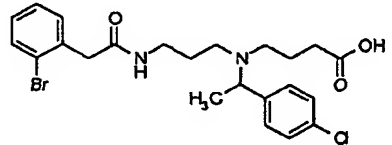
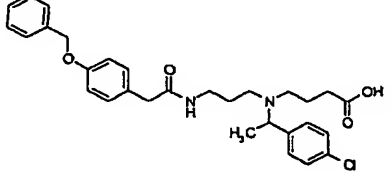
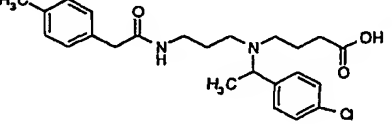
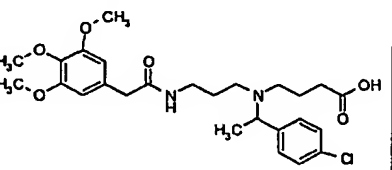
Compound 114, 4-[[3-[2-[4-(Benzyloxy)phenyl]acetylamino]propyl][(1S)-1-(4-bromophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner
5 to that described for compound 87 and contains the following characteristics:

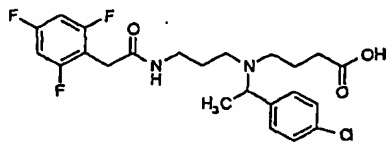
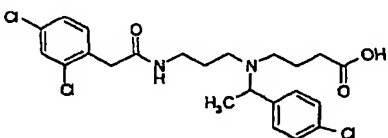
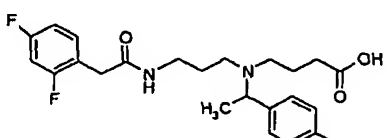
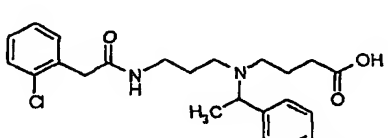
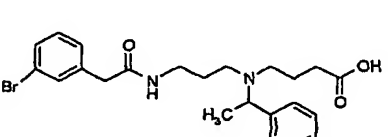
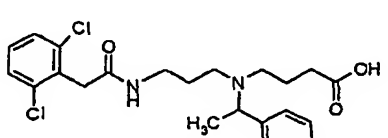
MS(ES⁺) m/e 569 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.15 (m, 11H),
6.92 (m, 2H), 5.03 (s, 2H), 4.08 (q, J=6.8Hz 1H), 3.44 (s, 2H), 3.21 (m, 2H),
2.74-2.52 (m, 4H), 2.40-2.25 (m, 2H), 1.85-1.60 (m, 4H), 1.47 (d, J=6.8Hz, 3H).

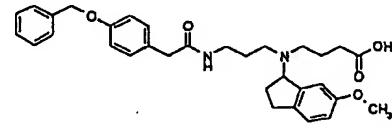
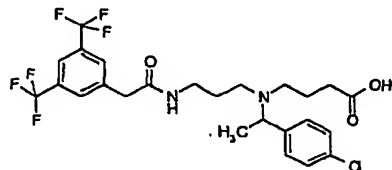
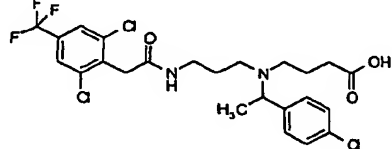
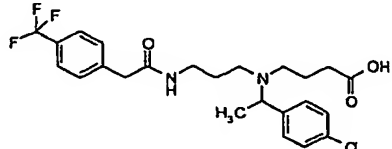
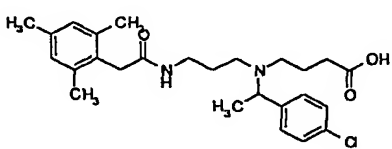
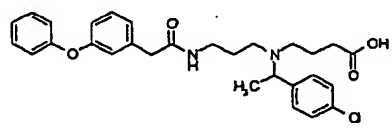
Compound 125, 4-[[3-[2-[4-(Benzyloxy)-3-
10 methoxyphenyl]acetylamino]propyl][(1S)-1-(4-chlorophenyl)ethyl]amino]butanoic
acid, can be obtained in an analogous manner to that described for compound 87 and
contains the following characteristics: MS(ES⁺) m/e 554 [M+H]⁺; ¹H NMR (400
MHz, CDCl₃) δ 7.42-7.22 (m, 9H), 6.84 (m, 2H), 6.72 (m, 1H), 6.61 (br, 1H),
5.10 (s, 2H), 4.02 (q, J=6.8Hz 1H), 3.86 (s, 3H), 3.43 (s, 2H), 3.20 (m, 2H),
15 2.67-2.28 (m, 6H), 1.78-1.64 (m, 4H), 1.40 (d, J=6.8Hz, 3H).

Compound 126, 4-[[3-[2-[4-(Benzyloxy)-3-
methoxyphenyl]acetylamino]propyl][(1S)-1-(4-bromophenyl)ethyl]amino]butanoic
acid, can be obtained in an analogous manner to that described for compound 87 and
contains the following characteristics: MS(ES⁺) m/e 599 [M+H]⁺; ¹H NMR (400
20 MHz, CDCl₃) δ 7.48-7.16 (m, 9H), 6.84 (m, 2H), 6.72 (m, 1H), 6.51 (br, 1H),
5.10 (s, 2H), 4.00 (q, J=6.8Hz 1H), 3.86 (s, 3H), 3.43 (s, 2H), 3.19 (m, 2H),
2.66-2.28 (m, 6H), 1.76-1.63 (m, 4H), 1.40 (d, J=6.8Hz, 3H).

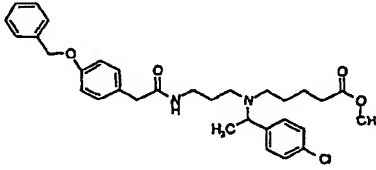
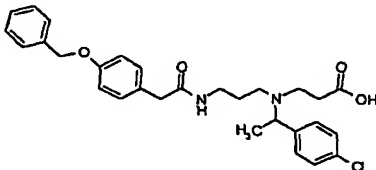
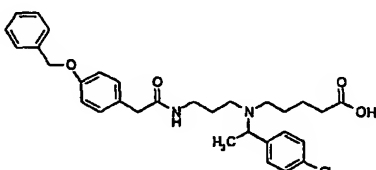
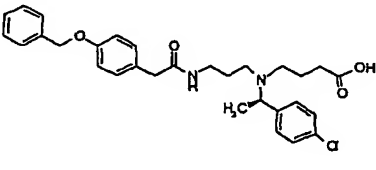
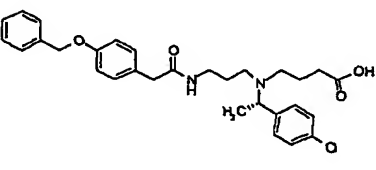
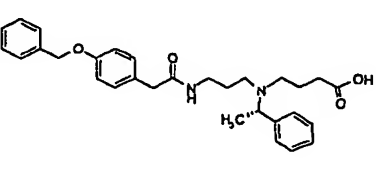
The following compounds, listed in Table 1D, were obtained in an analogous
25 manner to those of compounds described above.

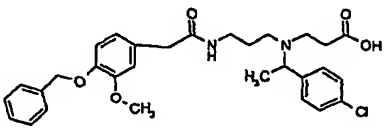
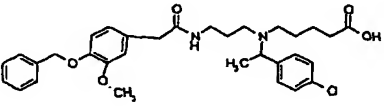
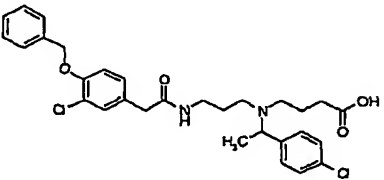
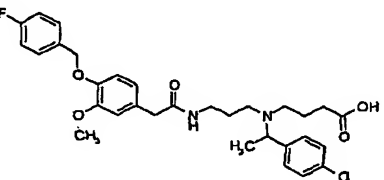
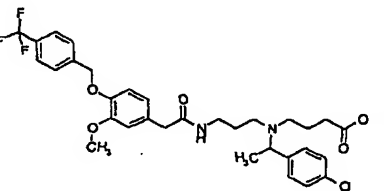
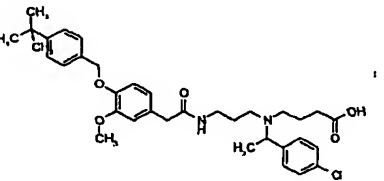
69		ES ⁺	477	[M+H] ⁺
70		ES ⁺	477	[M+H] ⁺
71		ES ⁺	496	[M+H] ⁺
72		ES ⁺	524	[M+H] ⁺
73		ES ⁺	431	[M+H] ⁺
74		ES ⁺	508	[M+H] ⁺

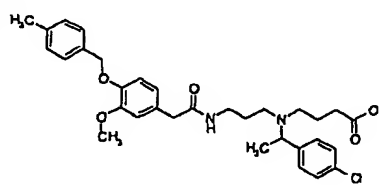
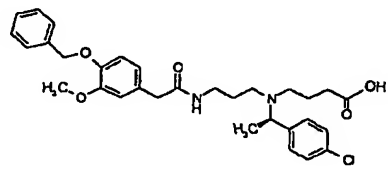
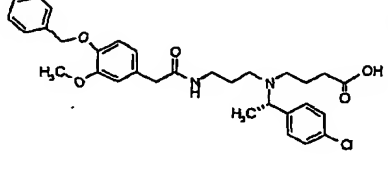
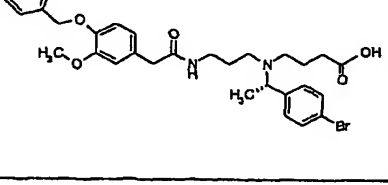
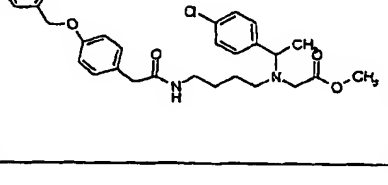
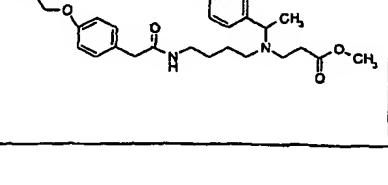
75		ES ⁺	471	[M+H] ⁺
76		ES ⁺	486	[M+H] ⁺
77		ES ⁺	453	[M+H] ⁺
78		ES ⁺	452	[M+H] ⁺
79		ES ⁺	496	[M+H] ⁺
80		ES ⁺	486	[M+H] ⁺

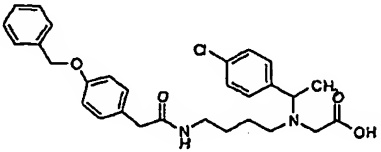
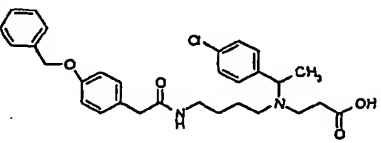
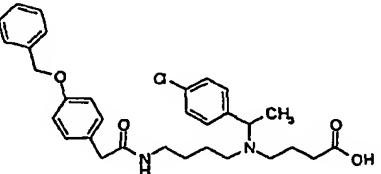
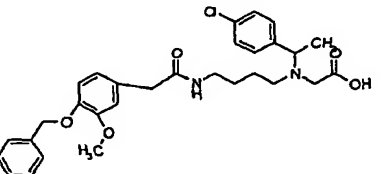
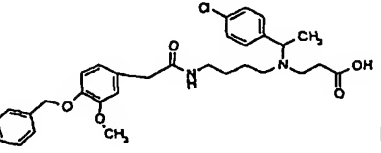
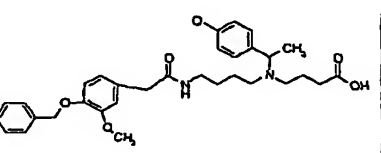
81		ES ⁺	531	[M+H] ⁺
82		ES ⁺	553	[M+H] ⁺
83		ES ⁺	554	[M+H] ⁺
84		ES ⁺	485	[M+H] ⁺
85		ES ⁺	460	[M+H] ⁺
86		ES ⁺	510	[M+H] ⁺

87		ES ⁺	553	[M+H] ⁺
88		ES ⁺	468	[M+H] ⁺
89		ES ⁺	468	[M+H] ⁺
90		ES ⁺	493	[M+H] ⁺
91		ES ⁺	536	[M+H] ⁺
92		ES ⁺	536	[M+H] ⁺

105		ES ⁺	552	[M+H] ⁺
106		ES ⁺	510	[M+H] ⁺
107		ES ⁺	538	[M+H] ⁺
108		ES ⁺	524	[M+H] ⁺
109		ES ⁺	524	[M+H] ⁺
110		ES ⁺	489	[M+H] ⁺

117		ES ⁻	540	[M+H] ⁺
118		ES ⁺	568	[M+H] ⁺
119		ES ⁺	558	[M+H] ⁺
120		ES ⁺	572	[M+H] ⁺
121		ES ⁻	622	[M+H] ⁺
122		ES ⁺	610	[M+H] ⁺

123		ES ⁺	568	[M+H] ⁺
124		ES ⁻	554	[M+H] ⁺
125		ES ⁺	554	[M+H] ⁺
126		ES ⁺	599	[M+H] ⁺
127		ES ⁺	524	[M+H] ⁻
128		ES ⁺	538	[M+H] ⁺

129		ES ⁺	510	[M+H] ⁺
130		ES ⁺	524	[M+H] ⁺
131		ES ⁺	538	[M+H] ⁺
132		ES ⁺	540	[M+H] ⁺
133		ES ⁺	554	[M+H] ⁺
134		ES ⁺	568	[M+H] ⁺

Compound No.	Inhibitory activity (%inhibition at 10 μ M)
6	100
7	100
8	100
9	99
10	97
11	96
12	100
13	88
14	97
15	97
16	94
17	94
18	95
19	98
20	95
21	95
22	92
23	93
24	94
25	88
26	98
27	84
28	86
29	96
30	50
31	97
32	33
33	25

Compound No.	Inhibitory activity (%inhibition at 10 μ M)
34	45
35	100
36	86
37	100
38	96
39	70
40	100
41	100
42	100
43	100
44	100
45	100
46	100
47	100
48	61
49	90
50	83
51	100
52	99
53	100
54	98
55	100
56	63
57	44
58	46
59	19
60	84
61	88

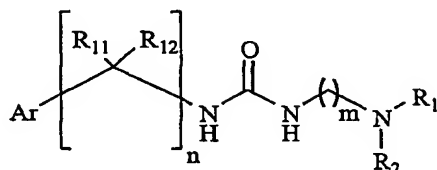
Compound No.	Inhibitory activity (%inhibition at 10 μ M)
62	97
63	100
64	40
65	69
66	85
67	83
68	93
69	71
70	36
71	67
72	99
73	87
74	44
75	64
76	72
77	75
78	46
79	85
80	95
81	22
82	97
83	78
84	73
85	96
86	100
87	100
88	100
89	100

Compound No.	Inhibitory activity (%inhibition at 10 μ M)
90	96
91	96
92	100
93	94
94	75
95	100
96	100
97	51
98	75
99	100
100	96
101	92
102	100
103	100
104	98
105	100
106	99
107	100
108	56
109	100
110	82
111	31
112	100
113	74
114	100
115	20
116	100
117	100

Twenty-four hours after eotaxin administration, bronchoalveolar lavage fluid (BALF) was collected by lavaging whole-lung three times with 0.7-ml aliquots of physiological saline containing 0.1% BSA via the tracheal cannula while gently massaging the thorax. The BALF recovered from one mouse was pooled,
5 centrifuged, and the cells were resuspended in 100 μ l saline containing 0.1% BSA. Cell numbers were determined using a hemocytometer and 2×10^4 cells were cytecentrifuged onto a glass slide. Cells were stained with Diff-Qick (International Reagent, Kobe, Japan), and cell types were identified by morphological criteria. Two hundred cells were examined per slide for differential count. As shown in
10 Figure 2., Compound 87 significantly suppressed eosinophil infiltration to BALF.

WE CLAIM

1. A compound of the Formula (I)



(I)

or a salt, hydrate, or stereoisomer thereof, wherein:

n is 0 or 1;

m is 2, 3, 4, or 5;

R11 and R12 are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl and heteroaryl

wherein the alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl,

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkoxycarbonyl, arylmethoxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

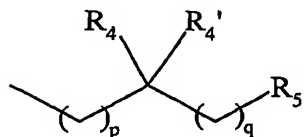
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

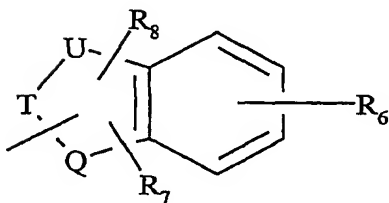
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino,
alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

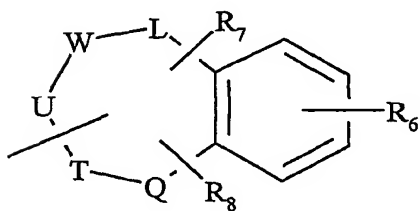
R₁ is:



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R₄ and R₄' are independently selected from the group consisting of hydrogen,
halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR₉; wherein R₉ is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino; R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl,

alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide,

arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and wherein no pair of said adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,

alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl,
 alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,
 arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
 alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,
 hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino,
 hydroxy, and halogen,
 cycloalkyl

optionally substituted with one or more groups independently
 selected from the group consisting of alkyl or alkoxy which is
 optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro,
 amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl,
 arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,
 alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl,
 alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,
 arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
 alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,
 hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino,
 hydroxy, and halogen,
 and heterocycle;
 provided that no bond is formed between R₁ and R₂.

2. The compound according to claim 1, wherein m is 3, 4, or 5.
3. The compound according to claim 2, wherein m is 3 or 4.
4. The compound according to claim 3, wherein Ar is aryl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl,

carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy.

5. The compound of claim 4, wherein R₂ is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acyloxy, acylamino, aryl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, aryloxy, arylmethyloxy, acylamino, hydroxy, and halogen, heteroaryl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

and cycloalkyl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,

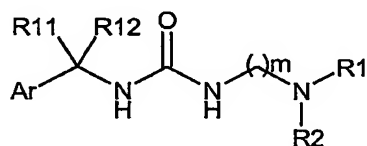
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
alkylsulfonamide, arylsulfonamide, and acylamino.

6. The compound of claim 5, wherein R₂ is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

7. The compound of claim 6, wherein R₂ is independently selected from the group consisting of alkyl, alkenyl and alkynyl, substituted with one or more groups independently selected from the group consisting of carboxy and alkyloxycarbonyl.

8. A compound of the Formula (II)



(II)

or a salt, hydrate, or stereoisomer thereof, wherein:

m is 2, 3, 4 or 5;

R₁₁ and R₁₂ are independently selected from the group consisting of hydrogen, halogen, C₁₋₅ alkyl, aryl and heteroaryl

wherein the alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkylloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

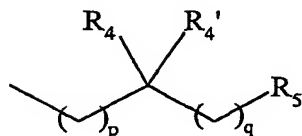
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl,

alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₁ is:



or

sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR₅; wherein R₅ is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino; R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may

form one or more double bonds, and wherein no pair of said adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,

alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl,
alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,
hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino,
hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently
selected from the group consisting of alkyl or alkoxy which may be
optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro,
amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl,
arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,
alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl,
alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,
hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino,
hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently
selected from the group consisting of alkyl or alkoxy which is
optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro,
amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl,
arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,
alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl,
alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,

hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino,
hydroxy, and halogen,
cycloalkyl

optionally substituted with one or more groups independently
selected from the group consisting of alkyl or alkoxy which is
optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro,
amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl,
arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,
alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl,
alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl,
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,
alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,
hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino,
hydroxy, and halogen,
and heterocycle;

provided that no bond is formed between R₁ and R₂.

9. The compound according to claim 8, wherein m is 3, 4, or 5.

10. The compound according to claim 9, wherein m is 3 or 4.

11. The compound according to claim 10, wherein Ar is aryl optionally
substituted with one or more groups independently selected from the group
consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy,
cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl,
carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl,
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide,
arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino,
guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy.

12. The compound of claim 11, wherein R₂ is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

and cycloalkyl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

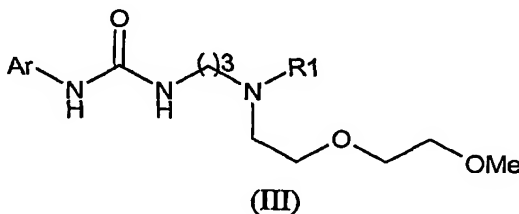
13. The compound of claim 12, wherein R₂ is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

14. The compound of claim 13, wherein R₂ is independently selected from the group consisting of alkyl, alkenyl and alkynyl, substituted with one or more groups independently selected from the group consisting of carboxy and alkyloxycarbonyl.

15. The compound according to claim 8, wherein the compound is defined in Table 1A.

16. A compound of the Formula (III)



or a salt, hydrate, or stereoisomer thereof, wherein:

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl,

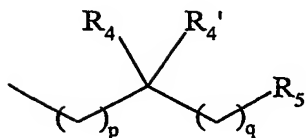
sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₁ is:



p is 0, 1 or 2;

q is 0, 1 or 2;

R₄ and R₄' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR₅; wherein R₅ is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino.

17. The compound according to claim 16, wherein Ar is aryl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl,

alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy.

18. The compound according to claim 16, wherein the compound is defined in Table 1B:

19. A pharmaceutical composition comprising a compound according to claim 1.

20. A method of treating CCR-3 mediated diseases in a patient, comprising administering to said patient an effective amount of the pharmaceutical composition of claim 19.

21. The method of claim 20, wherein said CCR-3 mediated disease is an eosinophil mediated allergic disease.

22. The method of claim 21, wherein said eosinophil mediated allergic disease is selected from the group consisting of asthma, rhinitis, eczema, inflammatory bowel diseases and parasitic infections.

23. The method of claim 20, wherein said CCR-3 mediated disease is a T-cell or a dendritic cell mediated disease.

24. The method of claim 23, wherein said T-cell or dendritic cell mediated disease is selected from the group consisting of autoimmune diseases and HIV.

25. The method of claim 20, wherein said pharmaceutical composition comprises a prodrug.

26. A kit for treating CCR-3 mediated diseases in a patient, comprising:
(A) the pharmaceutical composition of claim 19;
(B) reagents to effect administration of said pharmaceutical composition to said patient; and
(C) instruments to effect administration of said pharmaceutical composition to said patient.

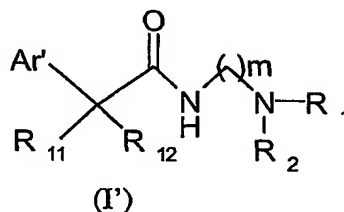
27. A method of inhibiting a CCR-3 mediated cellular response in a cell which expresses CCR-3, comprising contacting said cell with a compound according to claim 1, such that said cellular response is inhibited.

28. A method according to claim 27, wherein the CCR-3 mediated cellular response is an intracellular calcium mobilization.

29. A method according to claim 28, wherein the CCR-3 mediated cellular response is a chemotaxis.

30. A method of treating a CCR-3 mediated diseases in a mammal, comprising administering to said mammal an effective amount of the pharmaceutical composition according to claim 20.

31. A compound of Formula (I')



or a salt, hydrate, or stereoisomer thereof, wherein:

m is 2, 3, 4 or 5;

R_{11} and R_{12} are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl and heteroaryl

wherein the C_{1-5} alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

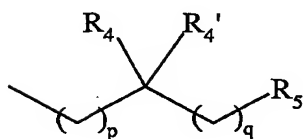
Ar' is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl,

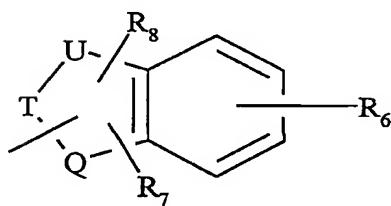
sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, heteroaryl, benzyloxy, benzoyl and naphthoyl

wherein the aryl, aryloxy, heteroaryl, benzyloxy, benzoyl or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

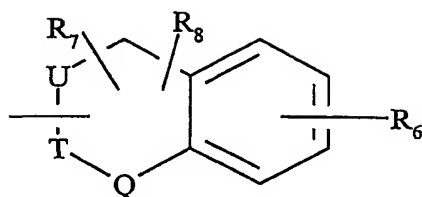
R₁ is:



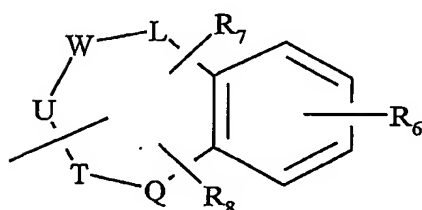
or



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R₄ and R₄' are independently selected from the group consisting of hydrogen, halogen, C₁₋₅ alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino

and COR₉, wherein R₉ is hydroxy, C₁₋₅alkyl, C₁₋₅alkoxy, amino, alkylamino or arylamino;

R₅ is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₆ is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino;

R₇ and R₈ are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and wherein no pair of said adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ alkenyl and C₁₋₈ alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide,

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C₃₋₇ cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of C₁₋₅ alkyl or C₁₋₅ alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that no bond is formed between R₁ and R₂.

32. The compound according to claim 31, wherein:
m is 3 or 4;

Ar' is aryl, optionally substituted with one or more groups independently selected from the group consisting of

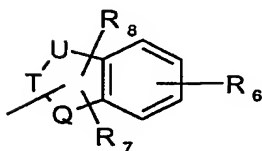
hydroxy, halogen, trihalomethyl, C₁-alkyl, C₁-alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, benzyloxy, benzoyl, and naphthoyl, wherein the aryl, aryloxy, benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of

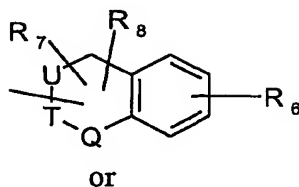
hydroxy, halogen, trihalomethyl, C₁-alkyl, C₁-alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

R₁ is:



or





p is 0 or 1;

q is 0 or 1;

R₄ and R₄' is

hydrogen,

halogen,

or C₁₋₃alkyl;

R₅ is aryl, optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R₆ is hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, or cyanoguanidino;

R₇ and R₈ is independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

Q, T, U, W and L is independently selected from the group of atoms consisting of C, N, O and S. Two adjacent atoms of Q, T, U, W and L may make double bond(s), and no pair of such adjacent atoms forms O-O or S-S;

R₂ is selected from the group consisting of C₁₋₃alkyl, C₁₋₃alkenyl and C₁₋₃alkynyl, wherein the C₁₋₃alkyl, C₁₋₃alkenyl or C₁₋₃alkynyl is optionally substituted with one or more groups independently selected from the group consisting of

carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, and cyano;

R₁₁ and R₁₂ are independently selected from the group consisting of hydrogen, halogen, and C₁₋₃alkyl.

33. The compound according to claim 32, wherein R₂ is selected from the group consisting of:

C₁₋₃alkyl, C₁₋₃alkenyl and C₁₋₃alkynyl, optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, alkylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido,

arylsulfonamido, sulfonyl, alkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano,;

wherein R₄, R₅, R₆, R₇, R₈, R₁₁, R₁₂, U, T, Q, p, and q are defined as in claim 32.

34. The compound according to claim 33, wherein U, T and Q are carbon atoms; p and q are 0; and R₁₁ and R₁₂ are hydrogen or C₁₋₃alkyl.

35. The compound according to claim 34, wherein Ar' is aryl, optionally substituted with one or more groups independently selected from the group consisting of:

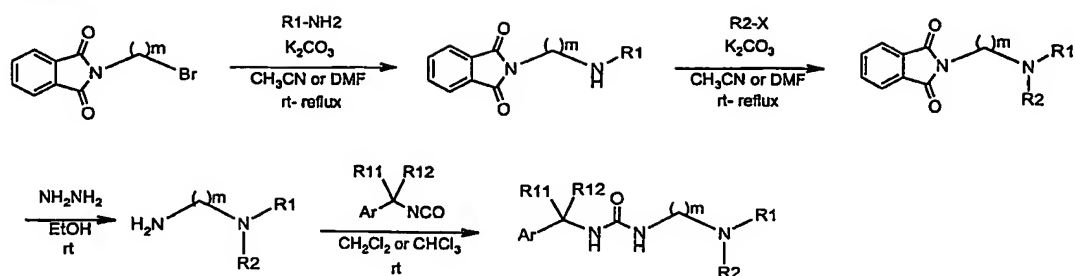
hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, nitro, amino, carboxy, benzyloxy, benzoyl, naphthoyl, aryl, wherein benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C₁₋₃alkyl, and C₁₋₃alkoxy.

36. A compound according to claim 31, wherein the compound is defined in Table 1D.

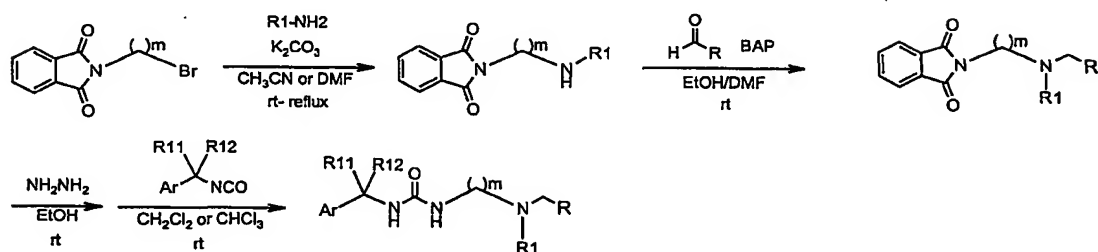
37. A pharmaceutical composition comprising a compound according to claim 31.

38. A method of treating a CCR-3 mediated disease in a patient, comprising administering to said patient an effective amount of the pharmaceutical composition of claim 37.

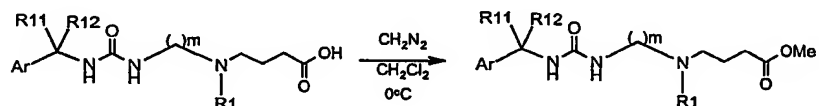
Scheme 1



Scheme 2



Scheme 3



Scheme 4



Scheme 5

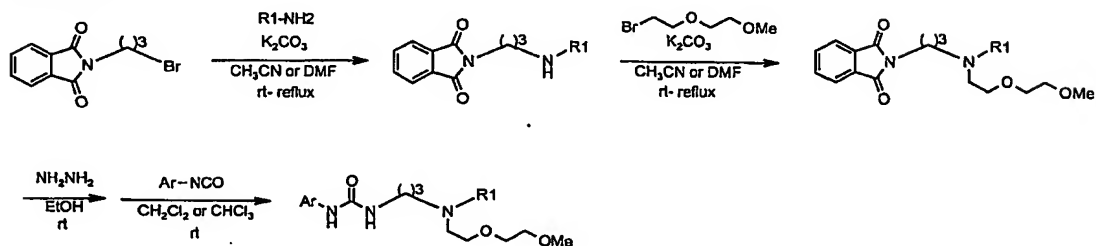
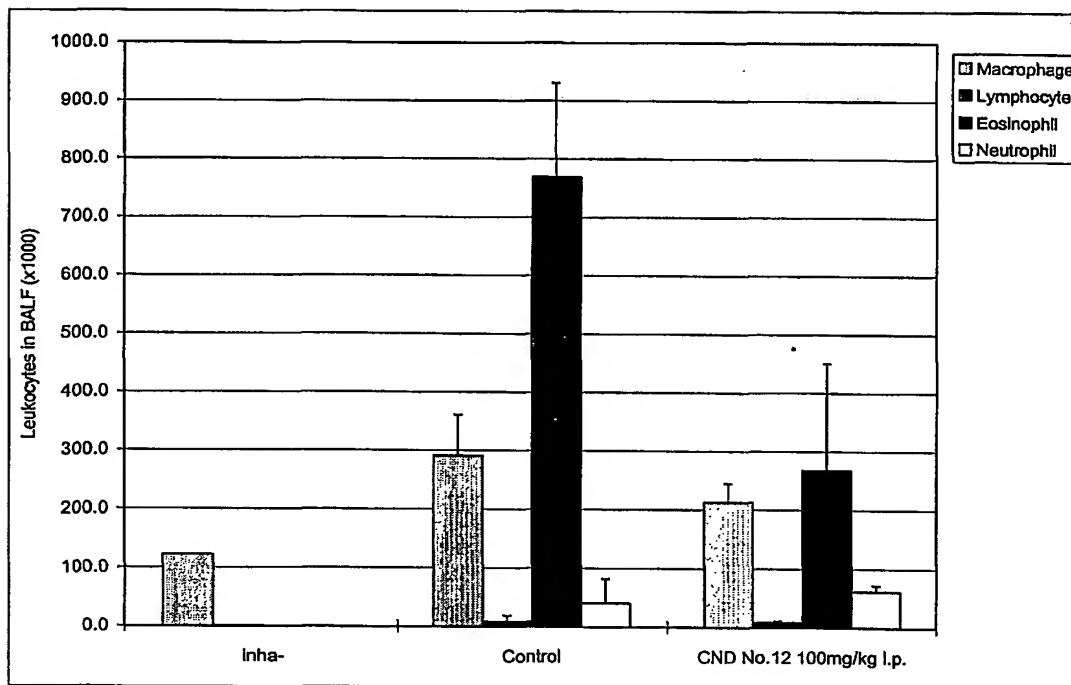
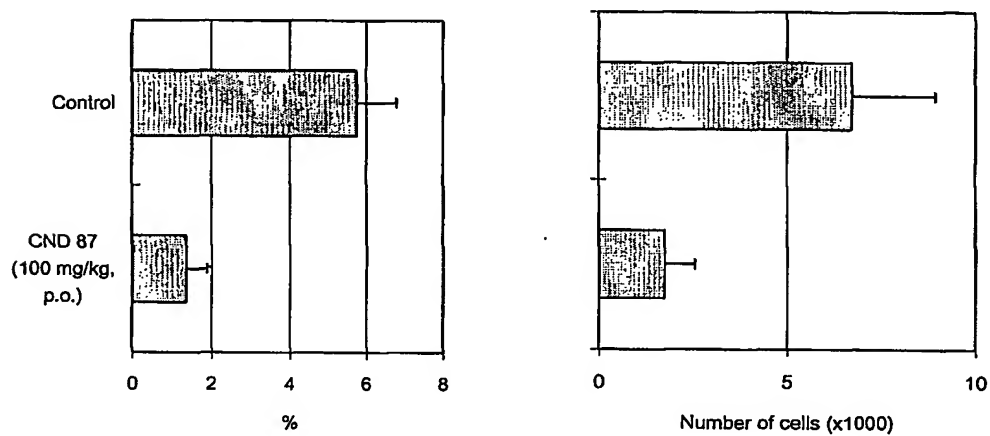


Figure 1. Suppression of Eosinophil Infiltration in Bronchoalveolar Lavage Fluid (BALF) by Compound No. 12



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Figure 2. Suppression of Eosinophil Infiltration in Bronchoalveolar Lavage Fluid (BALF) by Compound No. 87.



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